Effects Of Cerebral Blood Flow And $P_{ET}CO_2$ On Cognitive Function During Passive Heat Stress

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Abstract

This thesis tested whether cognitive performance during passive heat stress may be affected by changes in cerebrovascular variables as opposed to strictly thermally-induced changes. A pharmacological reduction in cerebral blood flow (CBF) using indomethacin along with a hypocapnia-induced CBF reduction during passive heat stress (T_{re} ~1.5°C above baseline) were used to investigate any cerebrovascular-mediated changes in cognitive performance. Repeated measures analysis of variance indicated that One-Touch Stockings of Cambridge (OTS) performance was not affected by a significant reduction in CBF during passive heat stress. More specifically, OTS accuracy measures did not change as a result of either a reduction in CBF or increasing passive heat stress. However, it was found that OTS response time indices improved with increasing passive heat stress independent of CBF changes. In conclusion, a significant reduction in CBF does not cause additional changes in performance of an executive functioning task during severe passive heat stress.

Key Words: heat stress, executive function, cognitive performance, cerebral blood flow.

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Table of Contents

List of Tables

List of Figures

List of Abbreviations and Symbols

ANOVA	Analysis of variance
BD	Body density
BF	Body fat
BP	Blood pressure
$\dot{C}$	Conduction
Ca_{O_2}	Arterial oxygen content
CBF	Cerebral blood flow
CBF_v	Cerebral blood flow velocity
CD_{O_2}	Cerebral oxygen delivery
$CMRO_2$	Cerebral metabolic rate
CO_2	Carbon dioxide
CO_x	Cerebral oxygenation
CRT	Choice reaction time
$\dot{E}$	Evaporation
ECA	External carotid artery

ECG	Electrocardiogram
FCS	First choice solved
FCL	First choice latency
GWT	Global Workspace Theory
HR	Heart rate
ICA	Internal carotid artery
IHE	Initial heat exposure
$\dot{K}$	Convection
LCG	Liquid conditioning garment
$\dot{M}$	Metabolic heat production
MAM	Maximal Adaptability Model
MCA	Middle cerebral artery
MCA_v	Middle cerebral artery velocity
MCC	Mean choice to correct
MLC	Mean latency to correct
NIRS	Near infrared spectroscopy

NSAID	Non-steroidal anti-inflammatory drug
O_2	Oxygen
OTS	One-Touch Stockings of Cambridge
P_aCO_2	Partial pressure of arterial carbon dioxide
PCO_2	Partial pressure of carbon dioxide
$P_{ET}CO_2$	Partial pressure of end-tidal carbon dioxide
PO_2	Partial Pressure of oxygen
$\dot{R}$	Radiation
RH	Relative humidity
$\dot{S}$	Heat storage
SD	Standard deviation
T-LIM	Thermal tolerance (limit)
T_c	Core temperature
T_{re}	Rectal temperature
$\bar{T}_{sk}$	Mean skin temperature
TC	Thermal comfort

TCD	Transcranial Doppler
TS	Thermal sensation
USG	Urine specific gravity
V_e	Ventilation
$\dot{W}_k$	Mechanical work

1 Introduction

The physiological effects of heat stress and hyperthermia on cognitive function have been well documented throughout history (Hancock et al., 2007; Pilcher et al., 2002). However, definitive conclusions regarding these effects remain inconsistent and contradictory. The differences in findings have been generally attributed to the conflicting nature of previous research methods. As outlined by Gaoua (2010), these inconsistencies can range from differences in task complexity and task type used in assessing cognitive function, the technique used to induce hyperthermia, and the overall intensity and duration of thermal stress test conditions.

Changes in cognitive function during hyperthermia can occur as a result of variations in skin and core temperature (Gaoua et al., 2012; Hancock & Vasmatzidis, 2003; Simmons et al., 2008). For example, with immediate and short duration heat exposure, rapid increases in skin temperature results in a feeling of unpleasantness, otherwise known as the alliesthesial effect (Cabanac, 1971). This disrupts the homeostatic balance within the body, causing additional attentional demands and competition for neuronal resources that impairs the successful completion of a concurrent complex cognitive task (Gaoua et al., 2012). Moreover, prolonged heat exposure causes a significant increase in core temperature above which can be adequately compensated by the body's homeostatic mechanisms (e.g. heat loss pathways). It has been proposed that increased attentional resource demand/depletion (Hancock, 1989; Hancock & Vasmatzidis, 2003) and/or limited conscious access to attentional resources (Baars, 1993) are the principal sources of cognitive failure during heat stress. With regards to *short* duration heat exposure (<30 min; eliciting acute changes in skin temperature without

concomitant rise in core temperature), it is widely accepted that cognitive decrements are caused by variations in skin temperature causing increased resource demands/depletion (Gaoua et al., 2012; Hancock & Vasmatzidis, 2003; Pilcher et al., 2002; Ramsey & Kwon, 1992). However, definitive conclusions regarding the potential mechanisms of cognitive decline during *prolonged* heat stress (> 30 min; eliciting significant changes in skin and core temperature) are more difficult to elucidate due to the numerous disruptions in physiological homeostasis that occur under these conditions.

In addition to the aforementioned concepts regarding cognitive decline during prolonged hyperthermia, recent findings have yielded another potential physiological hypothesis. One indirect result of heat stress is a hyperthermia-induced hyperventilation, which reduces arterial partial pressures of carbon dioxide (P_aCO_2) (Haldane, 1905). Kety & Schmidt (1948) first showed that the cerebral vasculature is highly sensitive to changes in P_aCO_2 such that hypocapnia will result in cerebral vasoconstriction and a subsequent decline in cerebral blood flow (CBF). It is possible that during prolonged, intense heat exposure, P_aCO_2 will be sufficiently reduced to instigate a significant decline in CBF and hence cerebral oxygen delivery (Brothers et al., 2009; Nybo et al., 2014). Therefore, it can be postulated that these aforementioned physiological disturbances in homeostasis accompanying hyperthermia may have a direct effect on concurrent cognitive processing. Unfortunately, current research has been unable to adequately discern the effect of specific cerebrovascular factors occurring with hyperthermia.

Therefore, to examine the potential role of changes in the cerebrovasculature on cognitive impairment with hyperthermia, the present experiment independently altered end-tidal carbon dioxide ($P_{ET}CO_2$; a surrogate for P_aCO_2) and CBF during passive heat

stress. Using a pharmacological intervention (indomethacin), it is possible to manipulate CBF and oxygen delivery without concomitant changes in other physiological variables. In addition, via the use of end-tidal forcing, $P_{ET}CO_2$ can be clamped at baseline (isocapnia) to prevent the natural decline in $P_{ET}CO_2$ with heat stress-induced hyperventilation. Through these methods, it is theoretically possible to partition what *physiological* perturbation is the most likely contributor to reduced cognitive performance during prolonged heat stress. Therefore, the purpose of the present study was to examine cognitive performance of individuals completing an executive functioning task during passive heat stress with and without concomitant changes in $P_{ET}CO_2$ and CBF.

2 Review of Literature

2.1 Hyperthermia

The ability to prolong exposure duration and uphold consistent performance levels requires equilibrium between heat production and heat dissipation (Casa, 1999). Hyperthermia is defined by the International Union of Physiological Sciences - Thermal Commission (Commission, 2001) as, "the condition of a temperature regulator when core temperature is above its range specified for the normal active state of the species" (p. 257). During exposure to high environmental temperatures and humidity levels, the body relies on conduction, convection, evaporation, and radiation as heat exchange pathways.

Ultimately, heat production must be matched by any combination of the four heat-loss pathways to maintain thermal homeostasis and is characterized by the heat balance equation. This can be expressed as:

$$\dot{S} = \dot{M} \pm \dot{W}_k \pm \dot{R} \pm \dot{C} \pm \dot{K} - \dot{E}$$

Where $\dot{S}$ is body heat storage, $\dot{M}$ is metabolic heat production, $\dot{W}_k$ is mechanical work, and $\dot{R}$, $\dot{C}$, $\dot{K}$, and $\dot{E}$ represent radiation, conduction, convection and evaporation, respectively. When it comes to high environmental temperature exposure, $\dot{S}$ will represent a positive value, or a gain in heat storage (Cheung, 2009). If this increase in heat storage cannot be mitigated through heat loss mechanisms, it will eventually lead to a state of hyperthermia within the body.

2.1.1 Hyperthermia and Cerebrovascular Dynamics

Hyperthermia has been shown to elicit dramatic changes in ventilation such that during prolonged heat stress there is an increased hyperventilatory response, or thermal hyperventilation. As first noted by Haldane (1905), hyperthermia elicits a pronounced increase in respiratory frequency and tidal volume. In turn, this thermal hyperventilation reduces arterial partial pressures of carbon dioxide (P_aCO_2), with an increase of ~1.5-2.0°C in core temperature reducing end-tidal partial pressures of carbon dioxide levels ($P_{ET}CO_2$) – a validated measure of P_aCO_2 during hyperthermia (Brothers et al., 2011) – by ~5-15 mmHg (Bain et al., 2014). However, an increase in core temperature of ~1.0°C must be elicited prior to observing any noticeable hyperventilatory response (Barltrop, 1954).

The resultant decrease in P_aCO_2 with hyperthermia also alters cerebral blood flow (CBF) and hence cerebral oxygen delivery (CD_{O_2}), which is a product of CBF and arterial oxygen content (Ca_{O_2})(Amann & Calbet, 2008). P_aCO_2 is widely regarded as one of the most influential factors in CBF regulation at both rest and exercise (Ide & Secher, 2000; Kety & Schmidt, 1948; Querido & Sheel, 2007; Willie et al., 2014). This phenomenon, termed "cerebrovascular CO_2 reactivity", is an index that describes the ability of the cerebrovascular arterioles to dilate or constrict relative to changes in P_aCO_2 (Ogoh & Ainslie, 2009). During hypocapnia (a physiological state of decreased P_aCO_2), the cerebral vasculature will vasoconstrict, subsequently reducing CBF. This mechanism is proposed to explain the attenuation of CO_2 washout from the brain in an attempt to maintain/increase P_aCO_2 levels (Ainslie & Duffin, 2009; Ogoh & Ainslie, 2009). Conversely, hypercapnia (a state of increased P_aCO_2) causes cerebral vasodilation thus

increasing CBF. This increase in CBF is suggested to aid in the washout of CO_2 from the brain and limits any further elevation in central P_aCO_2 (Ainslie & Duffin, 2009; Ogoh & Ainslie, 2009). Ainslie & Duffin (2009) has calculated that average global CBF reactivity is ~3.8%/mmHg change in P_aCO_2 within the eucapnic range of 35-55 mmHg. This cerebrovascular CO_2 reactivity is generally higher in the hypercapnic range (~3-6% increase in CBF/mmHg) as opposed to the hypocapnic range (~1-3% decrease in CBF/mmHg) (Ide et al., 2003; Sato et al., 2012; Willie et al., 2012; Willie et al., 2014).

As a result of these cerebrovascular changes in response to hyperthermia, CBF, indicated by a change in middle cerebral artery velocity (MCA_v), has been shown to decrease throughout a range of core temperatures. Fan et al. (2008) showed that with increasing core temperature, there is a concomitant reduction in CBF (+0.5°C = -6%; +1.0°C = -13%; +1.5°C = -23%; +2.0°C = -32%). These results are in agreement with numerous other studies (Brothers et al., 2009; Low et al., 2008; Nelson et al., 2011; Ogoh et al., 2013) that have found similar decrements in MCA_v with varying levels of hyperthermia.

Recently, it has also been suggested that hyperthermia may elicit reductions in CBF as a thermoregulatory response in an attempt to dissipate heat from the head, termed the thermoregulatory steal theory (Hasegawa & Cheung, 2013). In a study by Sato et al. (2011), it was found that moderate hyperthermia led to a reduction in MCA_v, by way of the internal carotid artery (ICA). Simultaneously, there was a rise in external carotid artery (ECA) flow, which feeds the blood vessels of the face and neck region. Unfortunately, because Sato et al. (2011) did not take any thermal measurements (core or skin temperature), it is difficult to confirm whether or not there is a correlation between

cerebral blood flow diversion and hyperthermia. In response to this, Bain et al. (2013) investigated whether there is a blood stealing mechanism by the ECA for thermoregulatory purposes during hyperthermia. Despite a 2.0°C increase in core temperature, it was found that there was no relationship between the large increases observed in the ECA (~250%) and the decreases in the ICA (Bain et al., 2013). These results all but refute the thermoregulatory steal theory; however, it does confirm that there is an increase in ECA blood flow with hyperthermia. This also confirms that despite decreases in other cerebral arteries with hyperthermia-induced hypocapnia, the ECA blood flow is remarkably well preserved (even increased), most likely for the purpose of heat dissipation.

In addition to the aforementioned physiological responses to hyperthermia, there is a likely increase in cerebral metabolic rate ($CMRO_2$) (Bain et al., 2014; South, 1958). As previously noted, with hyperthermia, there is a concomitant decline in CBF. A result of this change in CBF is a reduction in oxygen (O_2) delivery, which is ultimately counteracted by an increase in tissue O_2 extraction (Bain et al., 2014). This is due to O_2 extraction being inversely proportional to blood flow assuming $CMRO_2$ is constant. Unfortunately, because of this interaction, if CBF was reduced by >50%, the resultant O_2 extraction would be unable to sufficiently maintain $CMRO_2$ and cerebral oxygenation (CO_x) (Bain et al., 2014; Gjedde, 2005). As such, any potential increases in $CMRO_2$ will severely limit the CBF reserve available to adequately maintain CO_x. Therefore, Bain et al. (2014) hypothesized that with a potential increase in $CMRO_2$ of ~10% and concurrent tissue temperature increase of 2°C, CBF could be reduced by ~40-50% and still sufficiently maintain CO_x due to a compensatory increase in O_2 extraction. Beyond this

threshold of CBF reduction, O_2 extraction is at maximum capacity and can no longer adequately preserve CO_x.

In summary, it has been shown that hyperthermia can cause changes in physiological variables such as ventilation ($P_{ET}CO_2$) and cerebral hemodynamics (CBF/CO_x) (Figure 1). Furthermore, it is possible that these physiological changes have a direct affect on cognitive function when exposed to environmental temperatures causing hyperthermia.

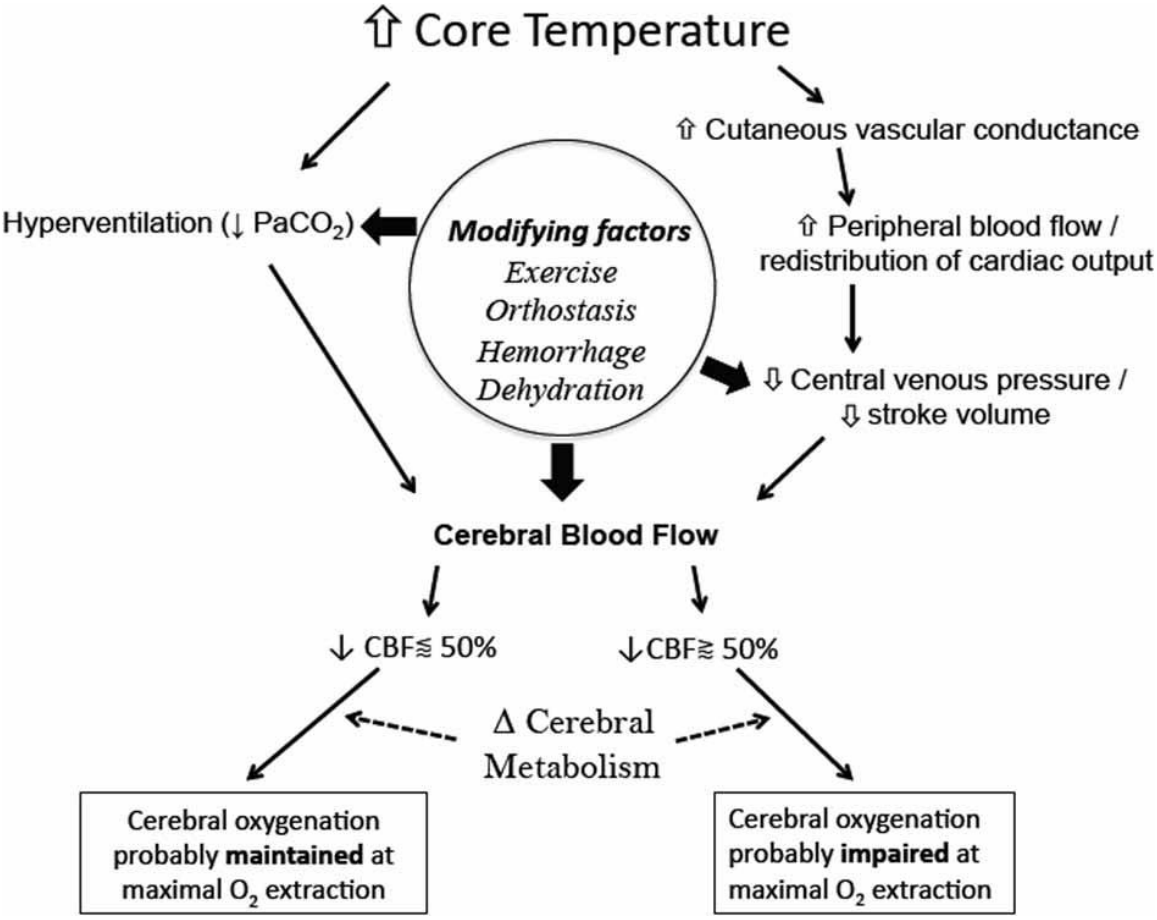

Figure 1. Schematic representation of the mechanisms and modifying factors causing changes in CBF and CO_x during whole-body hyperthermia (Bain et al., 2014).

2.2 Proposed Theories on Cognitive Performance and Thermal Strain

Current literature suggests that heat exposure causing hyperthermia is associated with marked reductions in cognitive ability (Gaoua, 2010). It has been proposed that these reductions are due to a number of possible mechanisms ranging from changes in arousal to depletion of attentional resources (Hancock & Vasmatzidis, 2003). Subsequently, various theories have been proposed in an attempt to explain the reduction in cognitive function during heat exposure.

2.2.1 Arousal Theory

The first and most widely used model of explaining the effects of hyperthermia on cognitive function is the Arousal Theory (Hancock & Vasmatzidis, 2003). This theory employs an inverted-U relationship to describe the relationship between arousal level and performance (Yerkes-Dodson Law). First described by Yerkes & Dodson (1908), the Arousal Theory (Figure 2) postulates that performance reaches a maximal point as arousal increases toward an optimal level (Hancock & Vasmatzidis, 2003). However, any further increase in arousal beyond this "optimal level" will elicit no further increases in quality of performance and, in fact, any movement away from optimal arousal levels will generate a subsequent decline in performance (Hancock & Vasmatzidis, 2003).

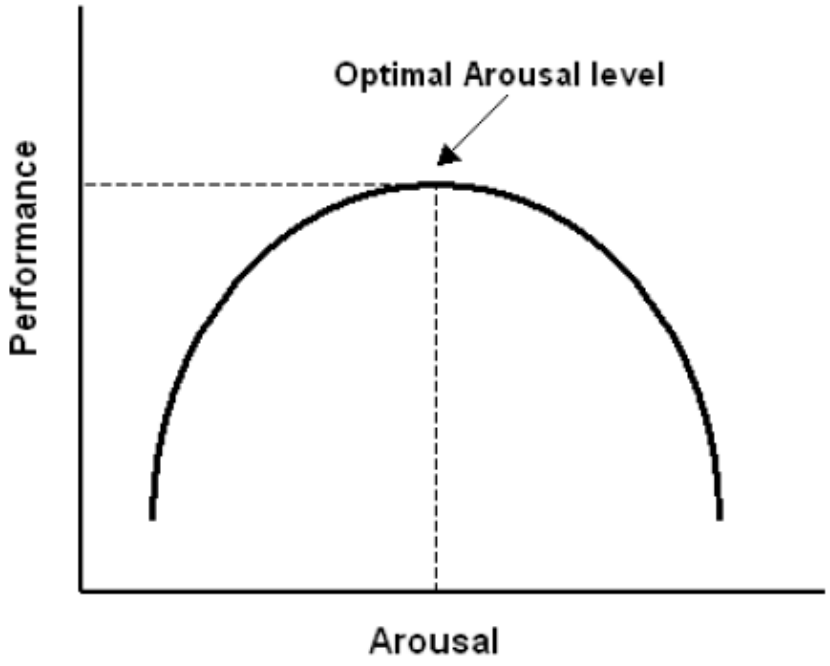

Figure 2. Arousal Theory as described by Hancock & Vasmatzidis (2003).

The inverted-U hypothesis has also been extended to explain the possible effects of thermal stress on performance as well (Griffiths & Boyce, 1971; Provins, 1966). As core body temperature rises above baseline levels, there is initially an associated increase in arousal level (Hancock & Vasmatzidis, 2003). However, in compliance with the inverted-U hypothesis, once a critical threshold in core temperature is reached, performance levels plateau and any further increase in core temperature (arousal) will result in performance decrements (Hancock & Vasmatzidis, 2003). As outlined by Hancock & Vasmatzidis (2003), Provins (1966) was the first to describe a potential relationship between the Arousal Theory and performance during heat stress. Provins (1966) argued that the Arousal Theory provided the means to consider both the environmental stressor as well as the psychological cost of completing the task, such that the collective cost of the

environmental/task combination represents the total degree of arousal. This relationship has been eloquently displayed in Hancock & Vasmatzidis (Hancock & Vasmatzidis, 1998)(Figure 3).

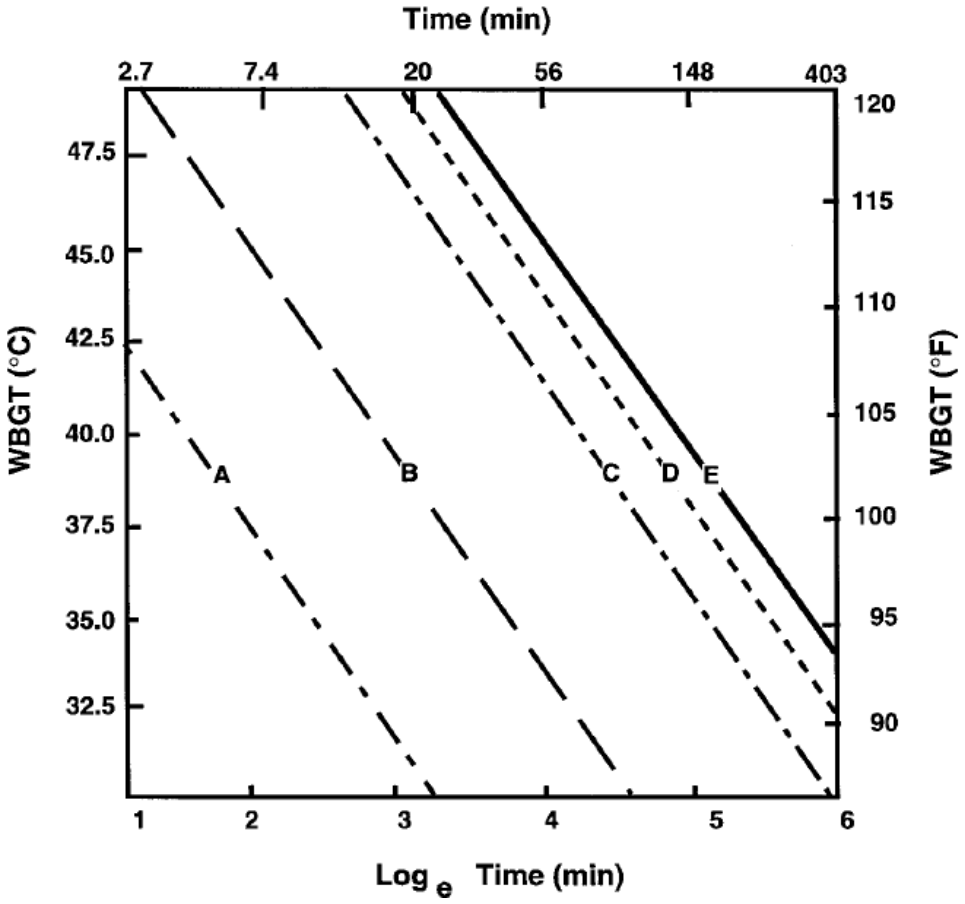

Figure 3. Human performance limits with Wet Bulb Globe Temperature (WBGT)/Log_e (Time). Line representation: A – vigilance performance; B – dual-task performance; C – tracking performance; D – simple task performance; E – physiological tolerance (Hancock & Vasmatzidis, 1998).

2.2.2 Maximal Adaptability Model and Global Workspace Theory

The Maximal Adaptability Model (MAM) and Global Workspace Theory (GWT) are two other theories regarding cognitive performance and thermal stress, respectively. These theories can be loosely grouped together as they are both based on the premise that humans only possess a limited amount of cognitive resources available to distribute at any moment.

The MAM, originally described by Hancock (1989), postulates that observed performance decrements are the direct result of external competition for, and subsequent depletion of, attentional resources due to added heat stressors (Kahneman, 1973). Within this framework (Figure 4), Hancock & Vasmatzidis (2003) outline stress levels ranging from low (hypostress) to high (hyperstress), respectively with a multitude of different threshold zones lying between these two extremes. At the epicenter of this stress level continuum lies the "normative zone", wherein the individual is able to complete all tasks without any necessary compensatory actions (Hancock & Vasmatzidis, 2003). Beyond this normative zone lies the "comfort zone", wherein cognitive tasks may be completed with only minimal adjustments needed to address the specific demands of the task (Hancock & Vasmatzidis, 2003). Hancock & Vasmatzidis (2003) state that as stress levels begin to increase beyond the comfort zone (through changes in duration or intensity of the stressor), there is a progressive decline in attentional resources. During this period of minimal stress (thermal), performance may be maintained or even increased due to the implementation of adaptive strategies to effectively use the remaining resources (Easterbrook, 1959). However, as stress levels continue to rise, the eventual depletion of attentional resources initiates cognitive function decline. The point at which

these cognitive decrements begin to occur is identified as the "psychological zone of maximal adaptability". Beyond this zone lies the "physiological zone of maximal adaptability," wherein any further increases in stress level begins to move the body away from its physiological homeostasis (Hancock & Vasmatzidis, 2003).

The MAM considers additional attention resource depletion during heat stress to be the cause of observed performance decrements. Furthermore, it allows for a correlation to be made between the magnitude of depletion in attentional resources and the onset of cognitive decline (Hancock & Vasmatzidis, 2003). The MAM is potentially a more useful and comprehensive model than the arousal theory with respect to thermal stress because, as Hancock & Vasmatzidis (2003) outlines, it is able to establish a relationship between both the psychological and physiological aspects of cognitive performance.

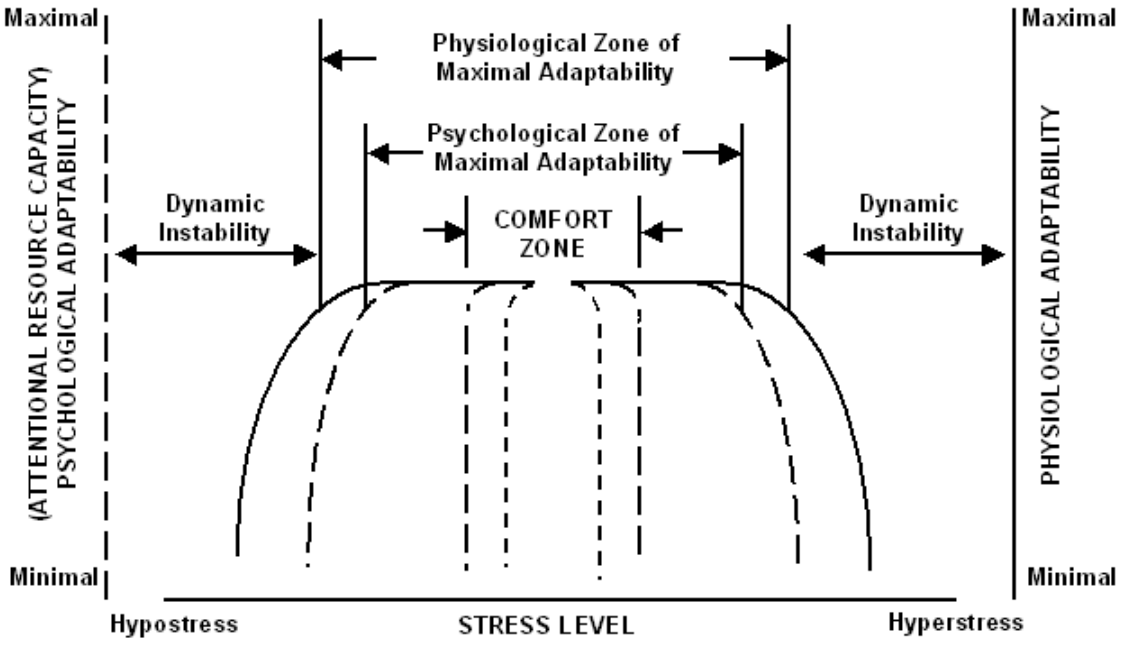

Figure 4. Maximal Adaptability Model as proposed by Hancock & Warm (1989).

Similarly to the MAM, the GWT (Baars, 1993) proposes that subconscious processes, such as temperature regulation, occur in conjunction with the completion of cognitive tasks. However, according to the GWT (Baars, 1993), conscious capacity is limited and acts to coordinate and manage neuronal resources for the unconscious processes. Subsequently, there is a limited resource capacity available to complete cognitive tasks due to multiple stimuli all competing for conscious access to the "global workspace" (Baars, 1993; Gaoua et al., 2012). It has been suggested (Gaoua, 2010) that during heat exposure there is an increased load placed upon a limited conscious workspace (task + thermal stress). As such, cognitive function becomes reduced once the available resources are insufficient to support both the cognitive task and imposed thermal load (Gaoua et al., 2012; Hocking et al., 2001).

2.3 Executive Functioning Performance and Heat Strain

Hancock & Vasmatzidis (2003) propose that cognitive function is primarily affected by dramatic alterations in the thermal state of the body. Decrements in cognitive performance have been observed during increases in both skin (Gaoua et al., 2011; Gaoua et al., 2012; Ramsey & Kwon, 1992) and core temperature (Simmons et al., 2008). However, the mechanisms through which these decrements occur are vastly different. With regards to peripheral temperature changes (skin), it appears that the rate of change is the primary factor in affecting concurrent cognitive performance (Gaoua et al., 2012). Alternatively, with central (core) temperature changes, both the rate of change as well as the absolute value has been show to be contributing factors in cognitive decline (Gaoua et al., 2011; Hancock, 1986; Hancock & Vasmatzidis, 2003).

2.3.1 Cognitive Performance and Core Temperature

A recent study by Simmons et al. (2008) examined the effect of increasing core temperature and skin temperature, both separately and combined, on cognitive performance during passive heat stress (45°C, 50% RH; core temperature = 1.0°C > baseline). To test this, participants were asked to perform four cognitive tasks (digit vigilance, choice reaction time, rapid visual information processing, and simple reaction time) during three different experimental conditions. It was found that independent increases in skin temperature did not elicit any changes in cognitive performance, whereas simultaneous increases in both skin and core temperature resulted in decreased cognitive performance, such that reaction times were increased but with a loss of accuracy. These results are in agreement with previous literature (Hancock, 1986) that suggests decrements in cognitive performance are only observed when core temperature is increased beyond a threshold at which the body can no longer adequately compensate. Further evidence of core temperature being an important regulating factor, was the recorded lack of change in cognitive performance during an alternative protocol within the same study examining head and neck skin cooling (Simmons et al., 2008). Simmons et al. (2008) found that skin cooling significantly reduced mean skin temperature, as well as feelings of thermal discomfort. However, despite these changes, core temperature remained at an elevated level and cognitive indices were unchanged when compared to pre-cooling performance values. These results suggest that core temperature is a more profound thermal limiting factor to cognitive performance, particularly with a *longer* duration heat exposure.

2.3.2 Cognitive Performance and Skin Temperature

Despite the reported results (Simmons et al., 2008), previous literature (Ramsey & Kwon, 1992) has also shown that cognitive decrements occur with *short* duration heat exposures (<30min). It is presumed that with such minimal exposure time, it is unlikely that observed cognitive impairments are due to vast alterations in core temperature. Taking these conclusions into account, it has been proposed (Hancock & Vasmatzidis, 2003; Pilcher et al., 2002) that cognitive function is also influenced, in large part, by skin temperature variations. These observed changes in cognitive function resulting from manipulations in skin temperature have been generally attributed to the alliesthesial effect. First described by Cabanac & Duclaux (1970), the alliesthesial effect proposes that a given thermal stimulus may induce feelings of pleasure or displeasure, depending on the ambient temperature. A stimulus is considered pleasurable when it facilitates adaptations within the body to return it to, or prevent further deviation from, its homeostatic state (Cabanac, 1971; Gaoua et al., 2012). Conversely, an unpleasant stimulus will begin to upset the homeostatic balance within the body (Cabanac, 1971; Gaoua et al., 2012).

In support of the alliesthesial effect theory, Gaoua et al. (2012) examined the hypothesis that an individual's subjective state, measured through changes in skin temperature, affects cognitive performance without a change in core body temperature. To do this, Gaoua et al. (2012) asked participants to complete a set of cognitive tasks while being exposed to two different environmental conditions; HOT (50°C/30%RH) and CON (24°C/30%RH). Participants were required to perform two distinct cognitive tasks; an executive planning task (One Touch Stockings of Cambridge – OTS) and a reaction

time test (Choice Reaction Time – CRT). Furthermore, there were two complexity levels (simple/complex) within each of the aforementioned tasks (OTS-4/OTS-6; CRT/5-CRT). Results from Gaoua et al. (2012) showed that there was a significant increase in skin temperature (+2.82°C) in the HOT vs. CON, with no significant difference in core temperature between the conditions. Furthermore, Gaoua et al. (2012) found that participants perceived themselves to be hotter, as indicated by an increase in thermal sensation, and less comfortable, indicated by an increase in thermal comfort, in the HOT condition compared to the CON condition. In regard to the cognitive testing, there were no significant differences in reaction time or accuracy measures between CRT and 5-CRT regardless of condition. Additionally, there were no significant difference in OTS-4 accuracy and latency measures. However, with the more complex OTS-6, performance was significantly better in the CON than the HOT condition (Gaoua et al., 2012).

Taking into account these results, Gaoua et al. (2012) proposed that the decrements seen in the OTS-6 during the HOT condition were most likely due to displeasureable feelings instigated by a sudden change in environmental conditions (alliesthesial effect). As outlined by Gaoua (2010), sudden changes in environmental conditions, such as heat exposure, may cause an additional cognitive load. This, in turn, increases the attentional demands leaving less available resources to successfully complete a concurrent cognitive task. Gaoua et al. (2012) revealed that exposure to the HOT condition, and subsequent ~3°C increase in skin temperature caused high feelings of displeasure, thus causing homeostatic imbalance within the body. Gaoua et al. (2012) further concluded that the observed decrements in cognitive function could not have been due to core temperature as there were no significant changes between conditions.

2.3.3 Combined effect of Skin and Core Temperature on Cognitive Performance

Gaoua et al. (2011) examined the effects of prolonged passive heat stress on neuromuscular and cognitive function. However, for the purpose of this literature review, the primary focus will be on the cognitive function testing. To test this, participants were required to perform identical experimental protocols in two different environmental settings. The control (CON) session required participants to enter an environmental chamber set at 24°C/40% RH and perform the OTS of different complexity levels (OTS-4 and OTS-6). The hot (HOT) session required participants to enter an environmental chamber set at 44°C/40% RH, however this ambient temperature was adjusted to ensure that participants core temperature reached a target value for each separate assessment period (T1 ~37.3°C; T2 ~37.8°C; T3 ~38.3°C; T4 ~38.8°C).

It was found (Gaoua et al., 2011) that OTS-4 results did not show any significant changes between conditions. However, OTS-6 results were significantly improved in CON condition vs. HOT condition (Figure 5). More specifically, it was observed that decrements in the OTS-6 occurred at the onset of heat exposure in participants with a normothermic core temperature. This suggests that complex cognitive performance can be affected by rapid changes in environmental temperature. As previously discussed, this sensitivity of cognitive function to changes in skin temperature could be partly related to the feelings of pleasure or displeasure that they induce (alliesthesial effect). Therefore, the increase in skin temperature observed at the onset of heat exposure generated an unpleasant stimulus that could be considered an additional cognitive load that draws upon the available resources. Subsequently, despite a rapid increase in skin temperature upon heat exposure (added cognitive load), there were sufficient attentional resources available

to successfully complete the less complex OTS-4 (Gaoua et al., 2011). Interestingly, during increased core temperatures at T2 (37.8°C) and T3 (38.3°C), there were no changes in cognitive performance regardless of OTS complexity (Gaoua et al., 2011). With regard to skin temperature, although there was a significant increase from T1, there was little variation in either the T2 or T3 assessment periods. Gaoua et al. (2011) suggested that this likely means the rate of change in skin temperature rather than the absolute temperature, is a more important factor when considering the effects on cognitive function.

During the final stage, T4 (38.8°C), complex task performance was significantly impaired (Gaoua et al., 2011). It has been previously suggested (Hancock, 1986) that cognitive performance decreases when there is a dynamic and uncompensable change in core temperature. Therefore, it was concluded that the decrements in cognitive function seen during the final stage were likely to have originated from the additional thermal load imposed by the dynamic changes in core temperature (Gaoua et al., 2011). As previously discussed, this finding is confirmed through the absence of detrimental effects on the OTS-4 results, which requires fewer resources to complete the task successfully, due to hyperthermia (Gaoua et al., 2011).

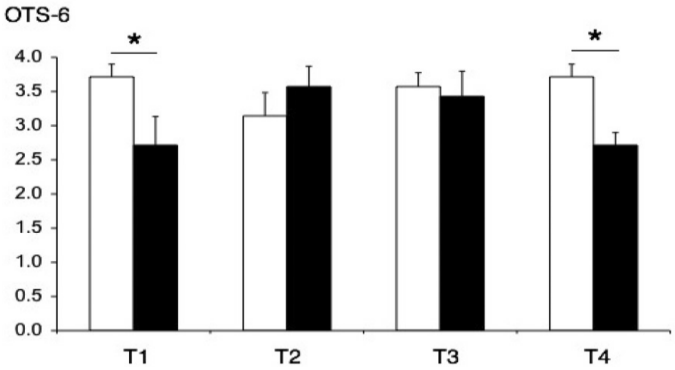

Figure 5. OTS-6 performance (CON – white; HOT – black) (Gaoua et al., 2011).

In summary, it would appear that cognitive function is affected by some combination of skin and core temperature. In the case of short duration heat stress (<30 min), where changes in core temperature have not yet been elicited, skin temperature appears to be a primary mechanism causing cognitive performance decline. Whereas, during longer, more intense heat exposure, it is generally accepted that core temperature has a stronger influence on cognitive function capabilities.

2.3.4 Possible Effects of $P_{ET}CO_2$ and Cerebral Blood Flow

It can be generally concluded that observed reductions in cognitive function upon initial heat exposure are likely due to the alliesthesial effect caused by rapid changes in skin temperature (Gaoua et al., 2011; Gaoua et al., 2012). However, the mechanisms causing cognitive decrements during heat stress of longer duration are more difficult to distinguish. Previous research has shown an increase in CBF during cognitive activation (Kelley et al., 1992; Szabo et al., 2011); therefore, it follows that an inhibition of CBF may cause a subsequent decline in cognitive performance. Previous literature examining cognitive function during heat stress has concluded that observed decrements in cognitive function are primarily due to thermal deviations from body homeostasis. That is, the additional thermal load as a result of alterations in skin and core temperature competes with cognitive resources required to complete complex tasks. However, previous literature has largely failed to consider the hyperthermic effect on ventilation (primarily the changes in $P_{ET}CO_2$ caused by hyperventilation). Moreover, this hyperventilation-induced hypocapnia causes cerebral vasoconstriction, which results in a significant reduction in CBF and oxygen delivery (Brothers et al., 2009; Nybo et al., 2014). Taking these effects into consideration, it is possible that cognitive decrements observed during

heat stress may be related to the changes in hypocapnia and subsequent alterations in cerebral hemodynamics. Due to the large influence of hyperthermia on ventilation ($P_{ET}CO_2$), and subsequently, the cerebral vasculature, it is plausible that any homeostatic disturbances in these variables ($P_{ET}CO_2$/CBF) may affect cognitive function during prolonged heat exposure.

A study by Schlader et al. (2013) examined the overall effects of hyperthermia on CBF during cognitive activation. Participants underwent cognitive testing (test of working memory – nBack test) during normothermic (34°C water perfusion - LCG) and hyperthermic (49°C) conditions. Hyperthermia was defined by Schlader et al. (2013) as an increase in core temperature by ~1.3°C. It was found that there was no significant change in CBF during cognitive activation with heat stress, which, in turn, had no negative effect on cognitive performance (Schlader et al., 2013). However, it was speculated by the authors (Schlader et al., 2013) that there were a multitude of reasons as to why this result occurred. First, it was hypothesized that the nBack cognitive test did not evoke the necessary cognitive overload necessary to elicit performance decrements with hyperthermia. Secondly, the hyperthermia-induced hypocapnia elicited in the study (Schlader et al., 2013) was relatively low (~4 mmHg). It is possible that such a minimal hypocapnic stimulus was not sufficient to evoke a strong cerebral vasoconstriction response, and subsequently there was only a moderate decrease in baseline CBF (~14%).

In another study, Ross et al. (2012) investigated the integrative effects of progressive, passive hyperthermia on CBF and alterations in motor drive. However, for the purpose of this literature review, only the hyperthermic effects on CBF and $P_{ET}CO_2$ will be discussed. During the study, experimental measurement were made at baseline

(37.1°C ± 0.3°C) and at 0.5°C increments in core temperature until participants reached their limit of thermal tolerance (39.1°C ± 0.4°C). Passive heating was achieved by circulating 50 ± 1°C water through a liquid conditioning garment. Ross et al. (2012) found that $P_{ET}CO_2$ gradually declined throughout heating as expected with increased ventilation (V_e) (occurring +1.0°C). However, $P_{ET}CO_2$ only became significantly different from baseline at an approximate 1.5°C increase in core temperature (Figure 6). Similarly, CBF_v, indicated by MCA_v, decreased throughout the heating protocol, becoming significantly different from baseline at +1.0°C. Furthermore, CO_x was significantly decreased from baseline measures at +2.0°C.

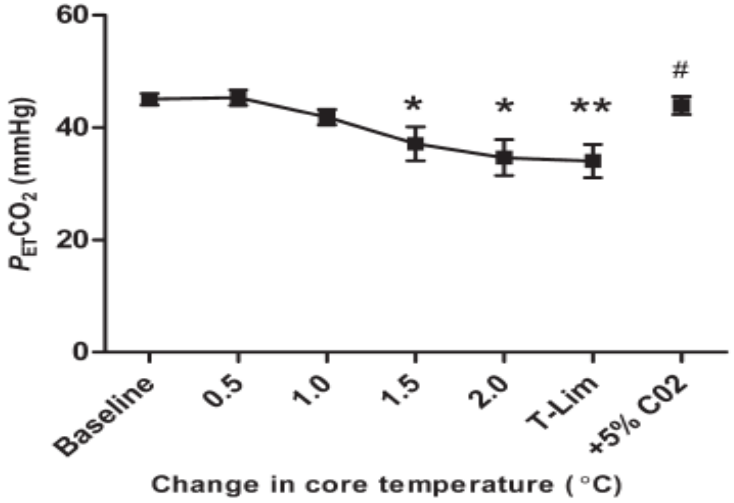

Figure 6. $P_{ET}CO_2$ changes with passive heat stress (Ross et al., 2012).

Examining the implications of Gaoua et al. (2011), Ross et al. (2012) and Schlader et al. (2013) provides a potential explanation of the observed cognitive decline during prolonged heat exposure. It is possible that more mentally demanding tasks (complex tasks) require a larger increase in CBF to support the metabolic demands (Schlader et al., 2013). With regard to Ross et al. (2012), they found that reductions in CBF only became

significant once core temperature had increased by 1.0°C above baseline values. Furthermore, $P_{ET}CO_2$ changes only became significantly different once core temperature had risen 1.5°C above baseline levels (~38.6°C). Similarly, with the study by Gaoua et al. (2011), cognitive decrements, apart from the initial exposure to heat stress, only occurred at a core temperature 1.5°C above baseline (~38.8°C). When integrating the results of these studies (Gaoua et al., 2011; Ross et al., 2012; Schlader et al., 2013), it appears that there may be a relationship between the observed decreases in $P_{ET}CO_2$/CBF and reductions in complex cognitive task performance with concurrent hyperthermia.

Research has shown that cognitive decrements occur with changes in skin (Gaoua et al., 2011) and core (Simmons et al., 2008) temperature. Recent results (Gaoua et al., 2011; Ross et al., 2012; Schlader et al., 2013) also suggest that changes in the cerebral vasculature during heat stress may also play a role in observed cognitive decline during prolonged heat stress. Ultimately, it is likely that changes in cognitive function with hyperthermia occur due to a multitude of physiological and psychological factors, and that these factors are symbiotic and not mutually exclusive.

2.4 Gaps in the Literature

2.4.1 Limitations of Previous Research

Current research examining the effects of hyperthermia on cognitive performance lacks a truly stressful heat stress protocol. With respect to Gaoua et al. (2011), it is possible that their study did not produce a stressful enough heat exposure to induce cognitive decrements at all time points. Having participants core temperature increase at such a gradual rate (0.5°C every 90 min) may not have produced a stressful enough

thermal strain to induce cognitive decrements during the middle stages. Similarly, although skin temperature gradually increased over the course of the entire trial, no cognitive decrements after T1 were attributed to increasing skin temperature. From this, Gaoua et al. (2011) ultimately suggested that it might be the rate of change rather than the absolute temperature that plays a more prominent role in cognitive performance.

Current research has not elicited a truly meaningful reduction in CBF as a result of hyperthermia-induced hypocapnia, which may be needed to induce a noticeable decline in cognitive function. As observed by Ross et al. (2012), changes in $P_{ET}CO_2$ only begin at ~1.5°C increase in core temperature with passive heat exposure, which would explain the minimal reduction in $P_{ET}CO_2$ observed by Schlader et al. (2013). Since there was not a significant decline in $P_{ET}CO_2$, there would be minimal change in the cerebral vasculature and therefore no substantial reduction in CBF.

Finally, previous research examining similar changes in the cerebrovasculature (Schlader et al., 2013) has not utilized an appropriate mental task during hyperthermia to adequately stress cognitive performance. It is imperative that a test battery utilizing a significant quantity of neuronal resources is administered in order to induce the necessary overload, or depletion, to elicit hyperthermia-induced decrements in cognitive performance.

2.4.2 Role of Indomethacin

The use of indomethacin as a pharmacological intervention is relatively novel in the literature when examining CBF. Indomethacin is a non-selective cyclooxygenase inhibitor that can effectively decrease CBF and alter the cerebrovascular CO_2 reactivity to

both hypo- and hypercapnia (Ainslie & Duffin, 2009). By using Indomethacin, it is possible to selectively decrease CBF without any concurrent changes in significant physiological variables. This allows for the independent manipulation of CBF and $P_{ET}CO_2$ with concurrent heat stress.

3 Thesis Objectives and Hypotheses

3.1 Objectives

The objectives of this study are:

1. Examine the effects of passive heat stress (T_{re} ~2.0°C above baseline) on simple vs. complex cognitive tasks.
2. Determine the effects of hyperthermia-induced hyperventilation and subsequent decline in $P_{ET}CO_2$ (hypocapnia) on simple vs. complex cognitive tasks.
3. Determine the separate effects of $P_{ET}CO_2$ and CBF via end-tidal forcing and a pharmacological intervention on simple vs. complex cognitive tasks with concomitant heat stress (Table 1). To identify the individual effects of $P_{ET}CO_2$, $P_{ET}CO_2$ will be clamped at baseline through end-tidal forcing to prevent the natural decline in $P_{ET}CO_2$ during hyperthermia-induced hyperventilation. To identify the individual effect of CBF, a pharmacological-induced reduction will be utilized (indomethacin).

3.2 Hypotheses

The hypotheses of this study are:

1. Complex cognitive task performance will be impaired post wash-in during the Indo trial only due to significant reductions in CBF.
2. Complex cognitive task performance will be impaired upon initial exposure to heat stress (no change in core temperature from baseline) independent of changes in $P_{ET}CO_2$, CBF or T_{re}.

3. Complex cognitive task performance will be reduced during the final stage of heat stress exposure (~2.0°C increase in core temperature from baseline) independent of changes in $P_{ET}CO_2$ or CBF.

Table 1. Physiological manipulations for each experimental condition.

Protocol	*Physiological Manipulation*		
Poikilocapnic Hyperthermia	↑ T_c	↓ CBF	↓ $P_{ET}CO_2$
Isocapnic Hyperthermia	↑ T_c	n/c CBF	n/c $P_{ET}CO_2$
Isocapnic Hyperthermia + Indomethacin	↑ T_c	↓ CBF	n/c $P_{ET}CO_2$

Increase (↑); Decrease (↓); No Change (n/c); Core Temperature (T_c)

4 Methods

4.1 Participants

Eight healthy males from Brock University and the surrounding community volunteered to participate in this study. The mean ± SD age, height, mass and body mass index were 26 ± 8 years, 176.8 ± 6.8 cm, 67.47 ± 8.68 kg and 21.5 ± 1.5 $kg \cdot m^{-2}$, respectively. Due to sex differences in cerebrovascular CO_2 reactivity, only males were recruited. Participants were also excluded if they had a diagnosed medical condition(s) (cardiovascular, respiratory, neurological), or any contraindications to non-steroidal anti-inflammatory drugs (NSAIDs).

4.2 General Methods

4.2.1 Skin Fold Measurements

Skin fold thickness was measured with a caliper at seven sites (triceps, subscapula, abdomen, supra-iliac crest, abdomen, thigh, and medial calf) with the results used to calculate body fat (BF) composition. BD = 1.11200000 – 0.00043499 (X_1) + 0.00000055 $(X_1)^2$ – 0.00028826 (X_3), where X_1 represents the sum of chest, axilla, triceps, subscapula, abdomen, suprailium, front thigh skinfolds and X_3 represents age (Jackson & Pollock, 1978). Once BD was obtained, it was then input into the following equation; %BF = [4.950 / BD ($kg \cdot m^{-3}$) – 4.500] x 100 (Siri, 1961).

4.2.2 Hydration Status

Before and after each experimental session hydration status was assessed by measuring urine specific gravity with a refractometer (PAL-10S, Atago, USA). A

euhydration threshold of ≤ 1.02 was used as a cut-off value (Armstrong, 2005). If participants exceed this predefined threshold they were asked to consume 0.5 L of water and hydration was reassessed 30min later. If euhydration was confirmed at this point, testing began. If participants were still not adequately hydrated the experimental session was rescheduled for a later date.

4.2.3 Temperature Measurements

During each experimental trial, rectal temperature (T_{re}) was continuously measured using a thin and flexible general-purpose thermistor (Mon-A-Therm Core, Mallinkrodt Medical), inserted (by the participant) 15 cm beyond the anal sphincter.

Mean skin temperature ($\bar{T}_{sk}$) was measured with flexible thermistors (PVC-T-24-190, OMEGA Environmental Inc.) taped to the skin and calculated using a four point weighted averages equation with thermistors placed on the chest, forearm, thigh and calf. $\bar{T}_{sk}$ = (T_1 x 0.3 + T_2 x 0.3 + T_3 x 0.2 + T_4 x 0.2), where T_1 = chest temperature; T_2 = forearm temperature; T_3 = thigh temperature; T_4 = calf temperature (Ramanathan, 1964).

4.2.4 Blood Pressure Measurements

Beat by beat blood pressure was calculated from the blood pressure waveform using finger photoplethysmography (Nexfin, bmeye), with a finger cuff placed directly over the middle finger on the left hand. Blood pressure measurements were used to ensure that physiological parameters remain within a safe range during experimentation.

4.2.5 Electrocardiogram

To measure heart rate, a 3-lead electrocardiogram (ECG; BioAmp, AD Instruments) was used. Lead sites were shaved and cleaned with rubbing alcohol prior to placement of the electrodes.

4.2.6 Middle Cerebral Artery Flow Velocity Measurements

Cerebral blood flow velocity in the middle cerebral artery (MCA) was measured non-invasively by a 2-MHz transcranial Doppler (TCD) ultrasound probe (ST3, Spencer Technologies), attached bilaterally to a headband and secured anterior to the zygomatic arch, rostral of the pinna. Doppler probes were placed over the temporal windows (near the ear) and remained in place throughout the experimental protocol. The MCA was used in the current study as measurements of MCA_v via TCD have been validated with prostaglandin inhibition during 100mg oral dose of indomethacin (Xie et al., 2006). Furthermore, previous research has revealed similar CBF changes in both the MCA and ACA during cognitive activation of a similar executive functioning task (Frauenfelder et al., 2004).

4.2.7 End-Tidal Gas Measurements

A soft silicone facemask was worn to collect expired gases for determining end-tidal partial pressure of oxygen ($P_{ET}O_2$) and $P_{ET}CO_2$ concentrations using a gas collection system. Participants were permitted to briefly remove the mask and drink if they required fluid during the experimental protocol. However, fluid ingestion was only encouraged to ensure participants reached the necessary ~2.0°C increase in T_{re}.

An end-tidal forcing system was used to control the desired $P_{ET}CO_2$ levels for the participant throughout each experimental condition. Measurements of the concentration of expired $P_{ET}CO_2$ are derived from a standard metabolic cart. These expired values were compared to the desired values and a computer subsequently controlled the delivery of the correct volume and concentration of oxygen, carbon dioxide, and nitrogen for the next breath. This is a commonly used approach for controlling breathing gases since it provides excellent control of inspired gas concentrations (Koehle et al., 2009).

To control for the influence of $P_{ET}CO_2$ on cerebral blood flow, $P_{ET}CO_2$ levels were allowed to either fluctuate naturally (poikilocapnia), which would reduce the $P_{ET}CO_2$ down to ~30-32 mmHg with hyperventilation, or the end-tidal forcing system was used to maintain $P_{ET}CO_2$ at resting baseline levels (isocapnia) during conditions (Steinback & Poulin, 2007).

4.2.8 Liquid Conditioning Garment

Participants wore a liquid conditioning garment (LCG; BCS 4 Cooling System, Allen Vanguard) consisting of 1/8" diameter Tygon tubing sewn over a close-fitting stretchable shirt covering the torso, arms, and legs. The head, hands, and feet were left uncovered. To promote maximum heat exchange between the skin and the garment, participants wore only shorts during the experiments. Inlet water temperature of the garment, with a flow rate of ~1.5 $L \cdot min^{-1}$, was controlled by a recirculating chiller/heater with a resolution of 0.1°C. During passive heating, a water temperature of ~50°C was used to increase T_{sk} up to ~40°C and T_{re} up to ~2.0°C above baseline or participant tolerance. Furthermore, an impermeable rain-suit was worn over the LCG and a thermal blanket placed on top of the participant during the experimental trial to prevent heat loss.

This approach of heating has been previously used for similar durations as those described in the current experiment (Ross et al., 2012).

4.2.9 Indomethacin

An indomethacin pill(s) was ingested at a dose of 1.2 $mg \cdot kg^{-1}$ body mass up to a maximum dose of 100 mg. The maximum daily dose of indomethacin is 200 mg (Canadian Pharmacists Association, 2013); however, a single dose of no more than 100 mg is advised. Indomethacin is a reversible and safe cyclooxygenase inhibitor (NSAID), which decreases cerebral blood flow without concomitant changes in metabolic rate, cerebral pH or plasma catecholamines. This unique feature makes indomethacin an ideal tool for investigating the effect of cerebral blood flow independent of the control of breathing in humans. The indomethacin dosage was supplemented with a 150 mg over the counter antacid (ranitidine; trade name Zantac) to counteract possible side effects of gastrointestinal stress. A 150 mg dose of ranitidine is typically used to treat acid reflux (Canadian Pharmacists Association, 2013).

4.2.10 Cognitive Function Testing

To examine executive function, the One-Touch Stockings (OTS) of Cambridge (CANTAB, Cambridge Cognition Ltd.) was administered (Appendix A). The specific test mode used in the current study was the 7-choice-24 mode. The OTS test display (Figure 7) consists of two separate illustrations containing three coloured balls (red, blue and green), which are presented so that they are perceived as stacks of balls in a stocking/sock suspended from a line (Cambridge Cognition Ltd., 2014). The OTS consists of two distinct testing sections. During the first portion of the test, the participant must use the

coloured balls in the lower display to reproduce the pattern presented in the upper display in the least amount of moves possible. The participant completed a round of testing that consists of four difficulty levels: one move, two moves, three moves, and four moves, respectively. The second part of the OTS test required the participant to work out how many moves it will take to solve the problem. They would then touch the corresponding box, with the indicated number of moves, to indicate their response (Cambridge Cognition Ltd., 2014).

The OTS has four distinct outcome measure: 1) the number of problems solved on the first choice (FCS); 2) latency to first choice (FCL); 3) mean choices to correct answer (MCC), and; 4) mean latency to correct answer (MLC). The OTS test took approximately 10 min to complete (Cambridge Cognition Ltd., 2014). OTS problems consisting of four (OTS-4) and six moves (OTS-6) to complete were examined to assess changes in simple (OTS-4) and complex (OTS-6) executive functioning performance.

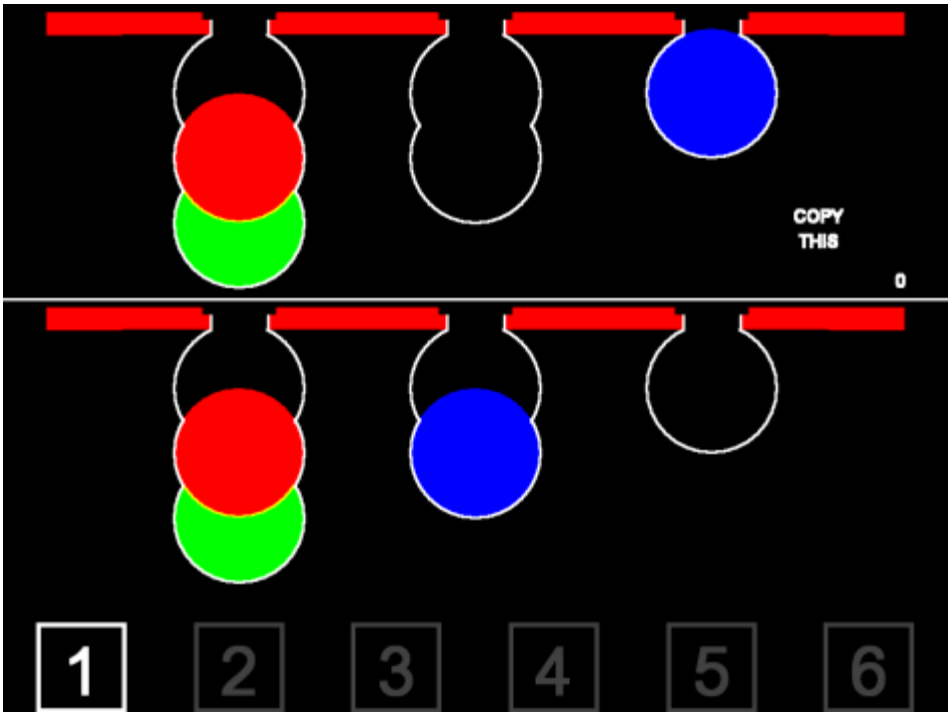

Figure 7. CANTAB – OTS Screen Shot.

4.2.11 Thermal Comfort/Thermal Sensation

To examine any potential changes in perceptual measures of the ambient temperature, values of Thermal Comfort (TC) and Thermal Sensation (TS) were taken at baseline, post wash-in, initial heat exposure (IHE) and thermal tolerance/limit (T-LIM). TC and TS were reported on 1-4 and 1-7 scales, respectively (Gagge et al., 1967).

4.3 Experimental Protocol

4.3.1 Screening Session

Before being allowed to participate, participants were asked to fill out a standard screening questionnaire detailing their current health status, use of medications and history of lung, heart, muscle and/or kidney disease (Appendix B). This questionnaire was completed in the presence of Dr. Matthew Greenway, MD, Ph.D.

4.3.2 Familiarization Session

For the familiarization session, participants underwent an entire experimental trial minus any of the specific manipulations. This session was to ensure that participants were comfortable with the heating protocol and consisted of passive heating using the LCG (water temperature ~50°C) to increase T_{re} by ~2.0°C or to T-LIM. During this session, participants were also familiarized with the OTS software and touchpad (performed the 7-choice-15 test mode).

4.3.2 Experimental Sessions

Upon arrival to the laboratory, participants began by changing into comfortable clothing (loose fitting t-shirt, pants/shorts) and provided a urine sample for hydration analysis. After ensuring adequate hydration, the rectal thermistor was self-inserted by the participants. When participants returned, a baseline 30 s Purdue Pegboard test was administered. Once completed, participants were instrumented with the LCG, skin temperature thermistors, a soft silicone mask for delivery of inspired air mixture and end-tidal gas concentrations, the finger blood pressure cuff, ECG, and TCD. During this instrumentation phase, participants were supine on a soft table. Upon instrumentation, participants underwent pre wash-in baseline testing consisting of baseline physiological measurements followed by completing the OTS cognitive test.

Participants then underwent the wash-in phase of the placebo (visits "a" and "b") or the indomethacin (visit "c"), the order of which was randomized. The wash-in period took ~90 min allowing sufficient time for the drug concentration to peak in the blood stream (Canadian Pharmacists Association, 2013). During this time participants and rested quietly in the lab.

Following the wash-in period, participants completed a second 30 s Purdue Pegboard test. Once this was completed, participants were exposed to (a) poikilocapnic hyperthermia (Poikilo), (b) isocapnic hyperthermia (Iso) or (c) isocapnic hyperthermia and indomethacin (Indo) interventions. During each condition, core temperature was passively increased until T-LIM or to a maximum of ~2.0°C. Cognitive testing was administered at baseline, post wash-in, IHE ($\geq$ 3.0°C in T_{sk}) and at T-LIM.

Immediately following the final experimental procedure, participants performed one last 30 s Purdue Pegboard test. Once this test was completed participants de-instrumented; however, they were monitored for 30 min throughout recovery to ensure that they were symptom free from any possible side-effects caused by the experimental protocol. All experimental procedures were performed with participants on a cushioned bench in a semi-recumbent position (~135° angle). Schematic overview of the experimental protocol is shown in Figure 8.

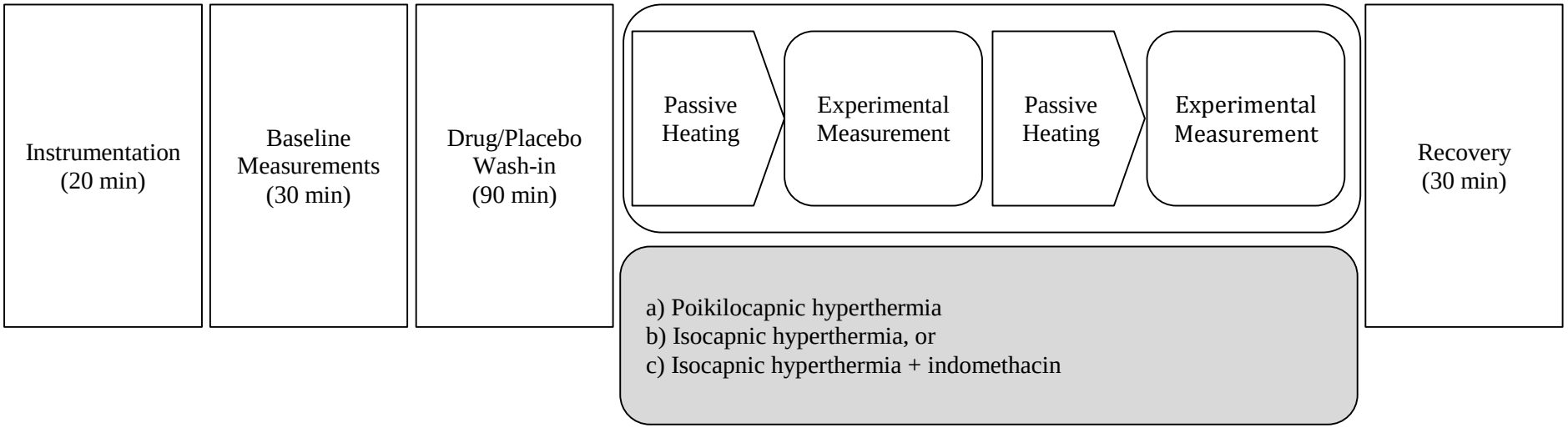

Figure 8. Schematic outline of experimental protocol.

4.4 Statistical Analysis

Individual two-way repeated measures ANOVA analyses were conducted to assess the change in respiratory, cerebrovascular, cardiovascular and cognitive responses between baseline, post wash-in, IHE and T-LIM across the three experimental conditions (Poikilo, Iso, Indo). Sphericity was assessed using Mauchly's test of sphericity, and if violated ($p \leq 0.05$), data was assessed using a Greenhouse-Geisser adjustment. Pair-wise comparisons, using a Bonferroni correction, were used to identify main effects. Any significant interactions (time x condition) were assessed using separate repeated measures ANOVA.

All statistical analyses were conducted using SPSS 20 (SPSS Inc., Chicago, Illinois, USA). Statistical significance was set at $p = 0.05$. Data is reported in text and tables as mean ± SD.

5 Results

All participants arrived at the laboratory in a euhydrated state (baseline USG, 1.012 ± 0.005); however, USG was slightly, but not significantly, increased at T-LIM (to 1.015 ± 0.003; $p = 0.14$). Body mass was significantly reduced from baseline to T-LIM (-2.2%; from 67.47 ± 8.68 to 65.98 ± 8.39 kg, $p < 0.001$). There were no significant differences in USG or body mass between conditions at any time point. Purdue Pegboard scores were unchanged across all conditions and time points.

5.1 Thermal and Perceptual Responses

No significant difference ($p > 0.05$) in baseline measurements were observed between conditions for T_{re}, $\bar{T}_{sk}$, TC or TS. Mean total heating time from post wash-in to T-LIM was 97.46 ± 35.49 min, during which time T_{re} increased by 1.48 ± 0.34°C ($p < 0.001$) from post-wash in (36.88 ± 0.27°C) to T-LIM (38.36 ± 0.37°C). Mean total heating time was moderately, but not significantly, lower in Indo (86.75 ± 36.19 min) when compared to Poikilo (102.00 ± 33.71 min, $p = 0.183$) and Iso (103.63 ± 38.64 min, $p = 0.132$) conditions.

5.1.1 Thermal Measures

T_{re} (Figure 9a) showed a significant main effect for time ($p < 0.001$) with no main effect for condition ($p = 0.177$) or significant interaction effect ($p = 0.303$). T_{re} was not significantly different between baseline (36.88 ± 0.27°C) and post wash-in (36.95 ± 0.26°C); however it was statistically different between post wash-in and IHE (36.86 ± 0.22°C, $p = 0.022$). Furthermore, it was also significantly higher at T-LIM (38.37 ± 0.37°C) relative to all other time points ($p < 0.001$).

Similarly, $\bar{T}_{sk}$, presented in Figure 9b, was not statistically different between baseline and post wash-in (32.43 ± 0.41 vs. 33.08 ± 0.43°C; p = 0.157); however, it was significantly increased relative to both baseline and post wash-in at both IHE (37.02 ± 0.35°C, p < 0.001) and T-LIM (39.21 ± 0.43°C, p < 0.001). Furthermore, $\bar{T}_{sk}$ was significantly different between IHE and T-LIM (p < 0.001). Changes in $\bar{T}_{sk}$ did not have a significant main effect for condition (p = 0.248) or a significant interaction effect (p = 0.767).

5.1.2 Subjective Measures

Thermal Comfort (Figure 9c) showed no interaction effect (p = 0.739) or main effect for condition (p = 0.657); however, there was a main effect for time (p < 0.001). TC was significantly increased at T-LIM compared to all time points (3.9 ± 0.2, p < 0.001). It was also statistically different between IHE (1.7 ± 0.6), post wash-in (1.1 ± 0.2; p < 0.006) and baseline (1.0 ± 0.0, p = 0.10); however, it remained relatively unchanged between baseline and post wash-in (p = 0.351).

Thermal Sensation (Figure 9d) only showed a significant main effect for time such that it was significantly increased at T-LIM compared to all time points T-LIM (6.9 ± 0.1, p < 0.001). Furthermore, IHE (5.4 ± 0.4, p < 0.001) was also significantly higher than baseline (3.8 ± 0.2, p < 0.001) and post wash-in (4.3 ± 0.4, p < 0.001); however, it remained unchanged between baseline and post wash-in (p = 0.153).

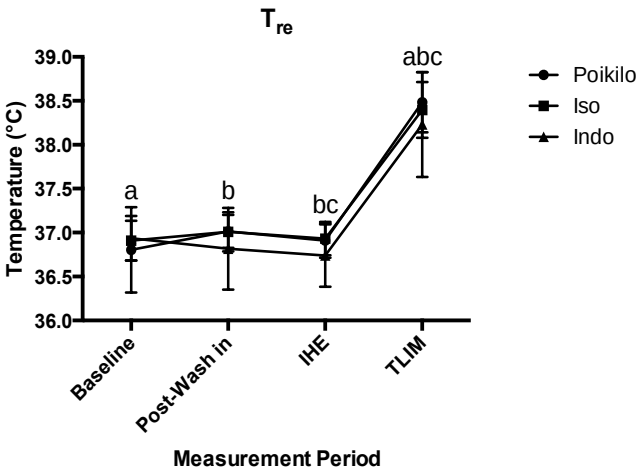

Figure 9a. Mean T_{re} with increasing passive heat stress between the three experimental conditions. Matching letters indicate significant differences between measurement periods ($p < 0.05$).

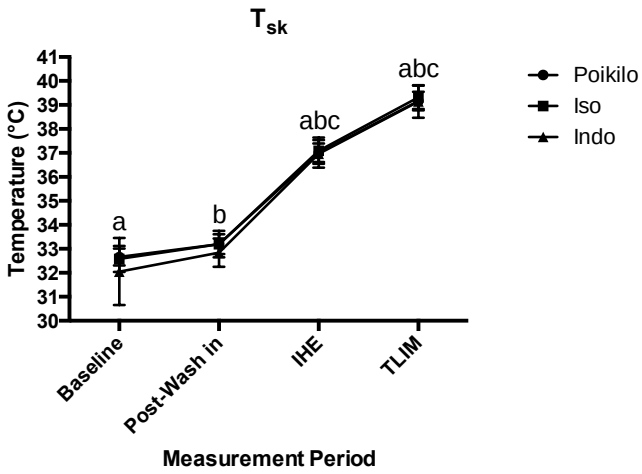

Figure 9b. Mean $\bar{T}_{sk}$ with increasing passive heat stress between the three experimental conditions. Matching letters indicate significant differences between measurement periods ($p < 0.05$).

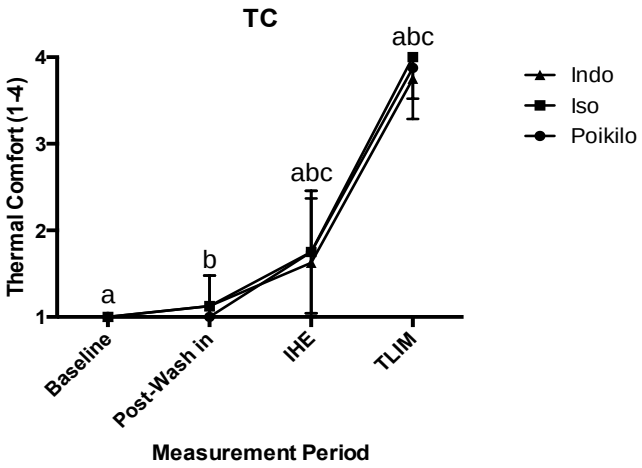

Figure 9c. Changes in TC with increasing passive heat stress across the three experimental sessions. Matching letters indicate significant differences between measurement periods ($p < 0.05$).

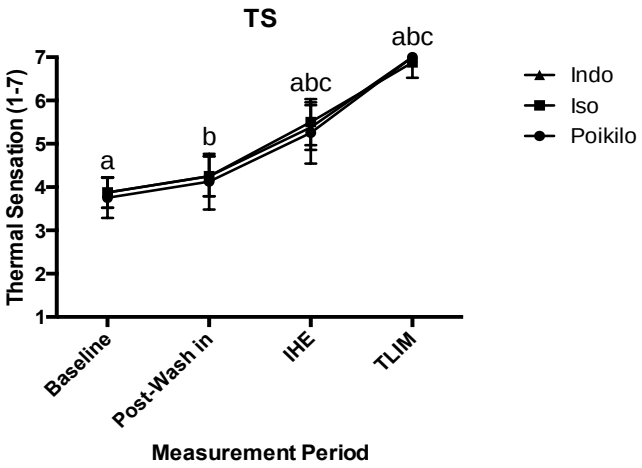

Figure 9d. Changes in TS with increasing passive heat stress across the three experimental sessions. Matching letters indicate significant differences between measurement periods ($p < 0.05$).

5.2 Respiratory, Cerebrovascular and Cardiovascular Responses

5.2.1 Respiratory Measures

V_e (Table 2) showed a main effect for time ($p = 0.015$); however did not display a main effect for condition ($p = 0.230$) or significant interaction ($p = 0.236$). Overall V_e was only significantly different at baseline when compared to all other time points ($p < 0.05$). Furthermore, V_e was only significantly different at T-LIM between Poikilo (17.49 ± 6.51 $l \cdot min^{-1}$) and Iso (24.38 ± 8.74 $l \cdot min^{-1}$, $p = 0.007$); it was not statistically different between Poikilo and Indo (21.13 ± 8.38 $l \cdot min^{-1}$, $p = 0.310$) or Iso and Indo ($p = 0.447$).

There was a significant interaction effect for $P_{ET}CO_2$ ($p = 0.006$)(Figure 10a) and a significant main effect for time ($p < 0.001$); however, no main effect for condition was found ($p = 0.397$). At baseline, $P_{ET}CO_2$ (Table 2) was not significantly different ($p > 0.05$) between all three conditions (46.01 ± 2.48 mmHg, 45.07 ± 1.70, 44.35 ± 3.42 mmHg for Poikilo, Iso and Indo respectively). Post wash-in, there was a significant reduction in $P_{ET}CO_2$ in the Indo condition (43.69 ± 2.46 mmHg) when compared to Poikilo (46.04 ± 1.87, $p = 0.021$); however, there was no significant difference between Poikilo and Iso (44.42 ± 3.73 mmHg, $p = 0.879$) or Iso and Indo ($p = 1.000$).

There were no significant differences ($p > 0.05$) between any of the conditions (44.53 ± 3.88, 45.02 ± 1.90, 43.43 ± 2.07 mmHg for Poikilo, Iso and Indo, respectively) upon IHE with respect to $P_{ET}CO_2$. At T-LIM, $P_{ET}CO_2$ was significantly reduced in the Poikilo condition (36.73 ± 3.59 mmHg) when compared to both Iso (42.75 ± 4.13 mmHg, $p = 0.015$) and Indo (41.21 ± 3.71 mmHg, $p = 0.034$). There was no statistical difference between Iso and Indo at T-LIM ($p = 1.000$).

5.2.2 Cerebrovascular Measures

MCA_v (Table 2) showed significant main effects for time ($p < 0.001$) and condition ($p < 0.001$) as well as a significant interaction effect ($p < 0.001$)(Figure 10b).

Similar values in MCA_v were measured at baseline between all three experimental trials (74.12 ± 6.10, 68.12 ± 6.66, 70.83 ± 7.87 $cm \cdot s^{-1}$ for Poikilo, Iso and Indo, respectively). In comparison to baseline values, MCA_v remained unchanged in Poikilo (73.41 ± 5.67 $cm \cdot s^{-1}$) and Iso (69.88 ± 6.34 $cm \cdot s^{-1}$) post-wash in ($p = 0.127$); however, MCA_v was significantly reduced in the Indo trial (46.42 ± 5.96 $cm \cdot s^{-1}$, $p < 0.001$).

With respect to IHE, MCA_v was significantly lower during the Indo trial (45.96 ± 5.53 $cm \cdot s^{-1}$) compared to both Poikilo (69.82 ± 6.97 $cm \cdot s^{-1}$, $p < 0.001$) and Iso (63.92 ± 6.95 $cm \cdot s^{-1}$, $p = 0.001$), with no significant differences between Poikilo and Iso ($p = 0.068$).

Finally, at T-LIM, MCA_v appeared to be lower in the Indo trial (46.07 ± 7.33 $cm \cdot s^{-1}$); however, this difference was not statistically different from either Poikilo (51.70 ± 6.39 cm·s-1, $p = 0.252$) or Iso (55.10 ± 6.87 $cm \cdot s^{-1}$, $p = 0.113$). There was also no significant difference between Poikilo and Iso conditions with regards to MCA_v at T-LIM ($p = 1.000$).

5.2.3 Cardiovascular Measures

HR showed significant interaction effect ($p = 0.004$)(Figure 10c), as well as significant main effects for time ($p < 0.001$) and condition ($p = 0.002$).

There were no significant differences between Poikilo (65.7 ± 13.1 $b \cdot min^{-1}$), Iso (66.4 ± 10.2 $b \cdot min^{-1}$), or Indo (66.0 ± 10.9 $b \cdot min^{-1}$) trials at baseline measurement ($p > 0.05$).

At post wash-in, HR was statistically significant between Indo (53.3 ± 6.2 $b \cdot min^{-1}$) and Poikilo (61.3 ± 8.7 $b \cdot min^{-1}$, $p = 0.007$), as well as Indo and Iso (62.5 ± 7.5, $p = 0.003$); however, it was not statistically different between Poikilo and Iso ($p = 1.000$).

Upon IHE, HR was again significant different between Indo (62.0 ± 8.1 $b \cdot min^{-1}$) and Poikilo (71.6 ± 9.8 $b \cdot min^{-1}$, $p = 0.032$), and Indo and Iso (73.1 ± 10.5 $b \cdot min^{-1}$, $p = 0.026$). HR was not statistically different between Poikilo and Iso at IHE ($p = 1.000$).

Finally, at T-LIM, HR was statistically different between Poikilo (114.4 ± 20.5 $b \cdot min^{-1}$) and Iso (125.0 ± 21.4 $b \cdot min^{-1}$, $p = 0.049$) as well as nearly significant between Iso and Indo (114.9 ± 17.2, $p = 0.052$); however, it there was no significant difference between Poikilo and Indo ($p = 1.000$).

Table 2. Respiratory and cerebrovascular responses to each experimental condition.

	Baseline	Post Wash-in	IHE	T-LIM
Poikilocapnia				
V_e, $L \cdot min^{-1}$	13.62 ± 3.87	16.18 ± 5.25	16.21 ± 5.73	17.59 ± 6.51
$P_{ET}CO_2$, mmHg	46.01 ± 2.48	46.04 ± 1.87	44.53 ± 3.88	36.73 ± 3.59[a]
MCA_v, $cm \cdot s^{-1}$	74.12 ± 6.10	73.41 ± 5.67	69.82 ± 6.97	51.70 ± 6.39[b]
Isocapnia				
V_e, $L \cdot min^{-1}$	17.13 ± 4.87	17.89 ± 4.14	19.18 ± 4.86	24.38 ± 8.74
$P_{ET}CO_2$, mmHg	45.07 ± 1.70	44.42 ± 3.73	45.02 ± 1.90	42.75 ± 4.13
MCA_v, $cm \cdot s^{-1}$	68.12 ± 6.63	69.88 ± 6.33	63.92 ± 6.95	55.10 ± 6.87[b]
Indomethacin				
V_e, $L \cdot min^{-1}$	12.68 ± 4.76	16.86 ± 2.47	17.74 ± 4.04	21.13 ± 8.38[a]
$P_{ET}CO_2$, mmHg	44.35 ± 3.42	43.69 ± 2.46	43.43 ± 2.07	41.21 ± 3.71
MCA_v, $cm \cdot s^{-1}$	70.83 ± 7.87[b]	46.42 +5.96	45.96 ± 5.53	46.07 ± 7.33

Values are expressed as means ± SD. [a]Significantly different from baseline ($p < 0.05$). [b]Significantly different from all other measurement periods ($p < 0.05$).

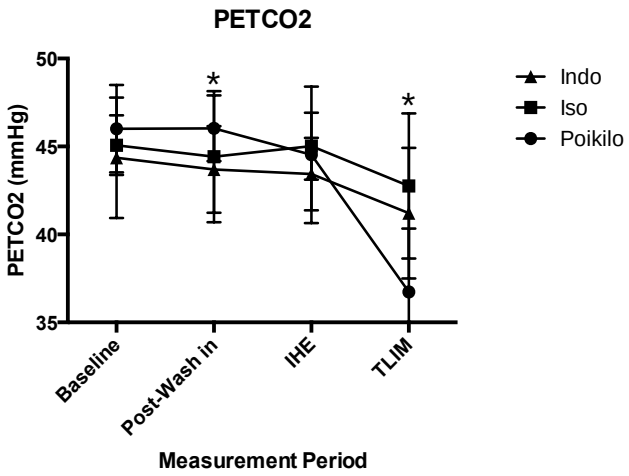

Figure 10a. Changes in $P_{ET}CO_2$ with increasing passive heat stress across the three experimental sessions. *Condition(s) significantly different from Poikilo ($p < 0.05$).

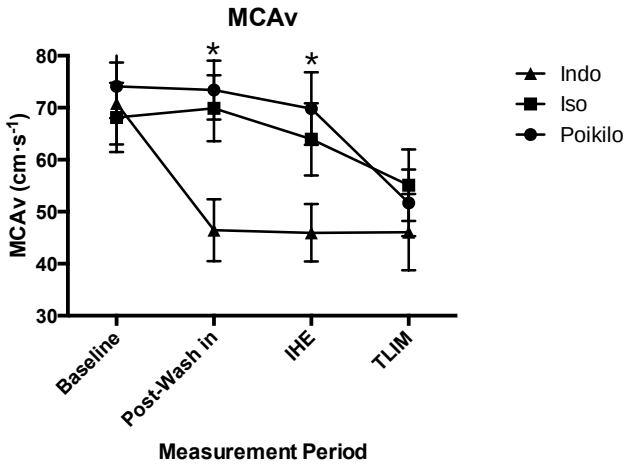

Figure 10b. Changes in MCA_v with increasing passive heat stress across the three experimental sessions. *Condition(s) significantly different from Indo ($p < 0.05$).

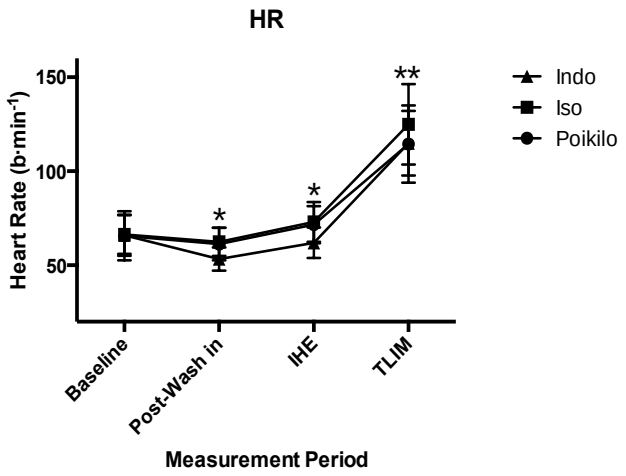

Figure 10c. Changes in HR with increasing passive heat stress across the three experimental sessions. *Condition(s) significantly different from Indo ($p < 0.05$). **Condition(s) significantly different from Iso ($p < 0.05$)

5.3 Cognitive Responses

5.3.1 OTS-4 Accuracy

FCS-4 (Table 3) showed no significant main effects for time ($p = 0.151$) or condition ($p = 0.921$) and displayed no significant interaction ($p = 0.974$).

MCC-4 (Table 3) showed no significant interaction effect ($p = 0.891$), or any significant main effects for time ($p = 0.055$) or condition ($p = 0.525$).

5.3.2 OTS-4 Response Time

FCL-4 (Table 3) showed a significant main effect for time ($p = 0.028$); however, there was no significant main effect for condition ($p = 0.656$) or interaction effect ($p = 0.612$). Overall post hoc analysis showed that FCL-4 was significantly faster at T-LIM (5792.54 ± 1697.53 ms) than at baseline (7721.50 ± 2474.33 ms, $p = 0.41$) and post-wash in (7009.45 ± 1939.26 ms, $p= 0.46$). Specifically, FCL-4 was only significantly different in the Poikilo condition between baseline (7005.44 ± 2994.79) and T-LIM (4065.09 ± 1251.79, $p = 0.026$).

There was a significant main effect for time ($p = 0.004$) when looking at MLC-4 (Table 3); however, there was no significant main effect for condition ($p = 0.588$) or significant interaction ($p = 0.481$). Overall post hoc analysis showed that MLC-4 was only significantly different at T-LIM (6916.44 ± 2449.99 ms) when compared to baseline (9656.03 ± 3538.33 ms, $p = 0.003$). Specifically, MLC-4 was only significantly different in the Poikilo condition between baseline (8588.06 ± 3676.74) and T-LIM (4376.22 ± 1182.70, $p = 0.040$).

Table 3. One-touch stockings of Cambridge performance (4 moves).

	Baseline	Post Wash-in	IHE	T-LIM
Poikilocapnia				
Problems solved on 1st choice	3.13 ± 0.99	3.5 ± 0.76	3.25 ± 1.16	3.5 ± 0.76
Choices to correct answer	1.34 ± 0.38	1.13 ± 0.19	1.22 ± 0.31	1.22 ± 0.25
Latency to 1st choice (ms)	7005.44 ± 2994.79	6559.09 ± 3702.22	7735.00 ± 6506.71	4065.09 ± 1251.79[a]
Latency to correct answer (ms)	8588.06 ± 3676.74	7458.94 ± 5155.44	8588.53 ± 6780.02	4376.22 ± 1182.70[a]
Isocapnia				
Problems solved on 1st choice	3.13 ± 0.99	3.5 ± 0.93	3.25 ± 0.71	3.13 ± 0.83
Choices to correct answer	1.34 ± 0.42	1.16 ± 0.30	1.28 ± 0.34	1.41 ± 0.38
Latency to 1st choice (ms)	8414.72 ± 4114.35	7112.50 ± 3389.46	7880.78 ± 3956.93	6545.03 ± 2926.15
Latency to correct answer (ms)	10100.59 ± 4603.94	7402.31 ± 3172.10	9144.03 ± 5731.15	8036.25 ± 4675.45
Indomethacin				
Problems solved on 1st choice	3.13 ± 0.99	3.5 ± 0.53	3.25 ± 0.89	3.25 ± 0.89
Choices to correct answer	1.31 ± 0.35	1.19 ± 0.22	1.28 ± 0.39	1.41 ± 0.40
Latency to 1st choice (ms)	7744.34 ± 3003.44	7356.75 ± 2556.44	7222.47 ± 4372.61	6767.50 ± 3672.14
Latency to correct answer (ms)	10279.44 ± 7193.89	7899.63 ± 2767.68	8356.50 ± 5361.63	8336.84 ± 6276.03

Values are expressed as means ± SD. [a]Significantly different from baseline ($p < 0.05$). No significant differences were observed between conditions within each measurement period.

5.3.3 OTS-6 Accuracy

There was no significant main effects for condition or significant interaction effect when examining FCS-6 (Table 4); however, there was a significant main effect for time ($p = 0.039$). Upon further examination of post hoc analysis, there were no significant differences between any time points.

MCC-6 (Table 4) had no significant interaction effect ($p = 0.725$) or main effect for condition ($p = 0.284$); however, there was a significant main effect for time ($p = 0.003$). Pairwise comparisons showed that MCC-6 was only significantly different between baseline (1.59 ± 0.38) and IHE (1.24 ± 0.22, $p = 0.045$).

5.3.4 OTS-6 Response Time

FCL-6 (Table 4) did not have a significant main effect for time ($p = 0.068$) or condition ($p = 0.52$); nor did it show any significant interaction effect ($p = 0.307$).

MLC-6 (Table 4) had a significant main effect for time ($p = 0.044$), but not for condition ($p = 0.596$). Furthermore, MLC-6 did not show a significant interaction effect ($p = 0.544$). However, despite MLC-6 being noticeably faster at T-LIM, further post hoc analysis did not show any significant differences between any time points.

Table 4. One-touch stockings of Cambridge performance (6 moves).

	Baseline	Post Wash-in	IHE	T-LIM
Poikilocapnia				
Problems solved on 1st choice	2.38 ± 1.30	3.75 ± 0.46	3.63 ± 0.74	3.00 ± 1.31
Choices to correct answer	1.47 ± 0.36	1.06 ± 0.12	1.09 ± 0.19	1.31 ± 0.44
Latency to 1st choice (ms)	23337.50 ± 17136.64	20461.22 ± 11111.75	16383.91 ± 9804.42	13982.38 ± 11593.44
Latency to correct answer (ms)	25450.79 ± 21276.05	17848.43 ± 9254.01	15449.91 ± 9720.79	15154.37 ± 12866.25
Isocapnia				
Problems solved on 1st choice	2.50 ± 1.20	2.25 ± 1.49	3.00 ± 1.07	2.50 ± 1.41
Choices to correct answer	1.69 ± 0.86	1.53 ± 0.53	1.34 ± 0.33	1.44 ± 0.46
Latency to 1st choice (ms)	31702.75 ± 32471.95	26264.06 ± 21670.86	19439.59 ± 11322.71	13644.16 ± 8299.46
Latency to correct answer (ms)	34668.09 ± 31522.13	28608.28 ± 21441.30	21763.34 ± 13288.04	15967.34 ± 8791.23
Indomethacin				
Problems solved on 1st choice	2.63 ± 0.92	3.25 ± 1.04	2.88 ± 1.36	2.63 ± 0.74
Choices to correct answer	1.63 ± 0.58	1.22 ± 0.31	1.28 ± 0.34	1.31 ± 0.26
Latency to 1st choice (ms)	19981.65 ± 13326.08	17643.62 ± 12387.67	22541.80 ± 14737.88	11810.35 ± 7171.53
Latency to correct answer (ms)	30463.97 ± 31795. 75	23245.50 ± 24360.28	25861.28 ± 20207.48	16357.75 ± 12204.41

Values are expressed as means ± SD. No specific significant differences were observed between conditions or measurement periods. Only *overall* significant differences were observed between measurement periods as discussed in text.

6 Discussion

The purpose of the present study was to examine cognitive performance of individuals completing an executive functioning task during passive heat stress with and without concomitant changes in CBF. This was accomplished through the combination of a pharmacological intervention (indomethacin) and dynamic end-tidal forcing to achieve the desired physiological manipulations. Based on previous psychophysiological research, it was hypothesized that both accuracy and response time indices of complex cognitive performance (OTS-6) would be diminished with IHE ($\bar{T}_{sk} \geq$ +3°C above baseline, n/c in T_{re}) as well as upon attainment of T-LIM (T_{re} ~1.5°C above baseline). Furthermore, it was hypothesized that OTS-6 would be affected by a reduction in CBF through hyperventilation-induced hypocapnia (due to hyperthermia) or via the pharmacological intervention (indomethacin). The main findings of this study are; 1) simple and complex OTS performance was unaffected by heat stress as well as reductions in CBF and $P_{ET}CO_2$ and, 2) improvements in OTS response time were associated with intensifying heat stress. These data suggest that, independent of thermal changes during passive heat stress, reduced CBF does not impair cognitive performance, specifically executive functioning.

6.1 Cognitive Performance and Heat Stress

A central finding of this thesis was that neither OTS-4 nor OTS-6 was affected with increasing passive heat stress. This lack of change in cognitive performance occurred despite significant increases in $\bar{T}_{sk}$, T_{re}, TC and TS from baseline/post wash-in levels to IHE and T-LIM. Measures of OTS accuracy (FCS/MCC) were relatively unchanged with

heat stress regardless of task complexity, with only MCC-6 being significantly different between post wash-in and IHE. OTS response time indices (FCL/MLC) were unchanged during OTS-6; however, overall OTS-4 response time markedly improved at T-LIM compared to baseline, post wash-in and IHE.

Consistent with these findings, previous research (Schlader et al., 2015) has shown that passive heat stress (T_{re} = +1.0-1.6°C) has a similar effect on OTS performance. Specifically, Schlader et al. (2015) found that, in younger adults, OTS response time improved while measures of accuracy remained unchanged. However, other studies (Gaoua et al., 2011; Gaoua et al., 2012) have found that passive heat stress inducing changes in $\bar{T}_{sk}$, increases in T_{re}, or both, resulted in diminished OTS performance. Furthermore, previous research (Gaoua et al., 2011; Gaoua et al., 2012) examining OTS performance during severe passive heat stress has also suggested that higher feelings of displeasure as a result of rapid increases in $\bar{T}_{sk}$ cause reduced cognitive performance; however, the present data fail to support this observation. However, despite increasing $\bar{T}_{sk}$, TS and TC (by 3.94 ± 0.32°C, 1.2 ± 0.3 and 0.6 ± 0.5, respectively) upon IHE (< 5 min of heat exposure) in the current study, accuracy and response time indices were relatively unchanged compared to values at post wash-in across all conditions. These contradictory and inconsistent results may be due, in part, to the heat stress protocol utilized. Similar to Schlader et al. (2015), the current study used water-perfusion suits (LCG) to induce passive heating as opposed to an overall environmental heat exposure as seen in other previous research (Gaoua et al., 2011; Gaoua et al., 2012). Schlader et al. (2015) reported that the contradictory results stem from the LCGs ability to tightly control temperature changes such that $\bar{T}_{sk}$ was maintained in their study during periods of

cognitive testing. This was opposite to that conducted in the Gaoua et al. papers (2011; 2012), where there was marked variation in $\bar{T}_{sk}$ due to the inability of an environmental chamber to precisely regulate thermal manipulations within the body. In the current study, there was no down-regulation of LCG flow during periods of cognitive testing; therefore, unlike Schlader et al. (2015), the OTS test was not performed during periods of stable $\bar{T}_{sk}$. However, despite this there were no significant changes in OTS outcomes measures.

Previous research (Gaoua et al., 2011; Gaoua et al., 2012; Hocking et al., 2001) has suggested that reductions in cognitive performance during heat stress stem from a competition for neuronal resources. However, the current data call into question previous assertions (Gaoua et al., 2011; Gaoua et al., 2012) regarding the effect of thermally-mediated changes complex cognitive tasks in cognitive function. Furthermore, the current results suggest that the brain's overall supply and ability to distribute these resources may not be as limited as previously thought. It appears that both simple and complex executive functioning tasks can be adequately completed despite dynamic instability within the body's thermal equilibrium. Previous research has also proposed (Gaoua et al., 2011; Gaoua et al., 2012) that cognitive performance decrements upon immediate exposure to heat stress may be due to the alliesthesial effect. This causes added attentional demands on a limited cognitive resource pool that is concurrently attempting to compensate for the sudden change in $\bar{T}_{sk}$. However, the results show that despite dynamic increases in $\bar{T}_{sk}$, and subsequently, higher feelings of displeasure (indicated by TC and TS) there were no changes in cognitive performance. This suggests that alterations in $\bar{T}_{sk}$ causing feelings of displeasure did not appear to draw a substantial

amount of neuronal resources from the existing supply pool. As such, dynamic $\bar{T}_{sk}$ changes may not play as significant of role in executive functioning tasks as previously thought (Gaoua et al., 2011; Gaoua et al., 2012).

The current data did reveal that there is a general trend towards improved OTS response time with increasing passive heat stress. It has been previously suggested (Gaoua et al., 2012) that this trend is likely to be a result of either an increase in nerve conduction velocity (Racinais et al., 2008) or an increase in impulsivity (Gaoua et al., 2011). The current findings suggest that this improvement in OTS response time is likely a result of both hypotheses. It has been previously shown (De Jesus et al., 1973; Johnson & Olsen, 1960; Lowitzsch et al., 1977) that nerve conduction velocity increases ~5% per °C change across a temperature range of 29-38°C (Kiernan et al., 2001). As such, it is possible that over the course of passive heating, conduction velocity could have increased upwards of ~30-40%. Since there were no significant changes in OTS accuracy measures in the current study, it is likely that participants did not become more impulsive with increasing heat stress. Rather, based on this lack of change in OTS accuracy indices, it is possible that participants simply benefitted from an increase in nerve conduction velocity that allowed them to select an answer more rapidly.

Ultimately, the current data suggest that heat stress coupled with concurrent executive functioning tasks may not be detrimental to the brain's ability to adequately distribute neuronal resources, as such it is possible to complete simple and complex tasks without much of a degradation in performance.

6.2 Cognitive Performance and CBF

A novel finding of the current study is that reductions in CBF are not associated with significant changes in cognitive performance. Despite significantly reducing CBF in the Indo trial at post wash-in (-26.99 $cm \cdot s^{-1}$/~36.77% and -23.46 $cm \cdot s^{-1}$/~33.57% when compared to Poikilo and Iso, respectively), OTS-4 and OTS-6 accuracy and response time was relatively unaffected (Table 3 and 4). Furthermore, a reduction in CBF with concurrent passive heat stress did not result in altered cognitive performance at either IHE or T-LIM. This suggests that, irrespective of changes in thermal indices ($\bar{T}_{sk}$, T_{re}, TC, TS), a reduction in CBF does not affect cognitive performance of an executive functioning task. These results further previous research (Schlader et al., 2013), which found no change in performance of a working memory task (nBack) despite a reduction in MCA_v. Contrary to previous research (Schlader et al., 2013), the current study utilized a pharmacological intervention to significantly reduce baseline CBF below what was seen in Schlader et al. (2013). However, despite inducing a greater magnitude of CBF reduction in the current study, it did not elicit any further reduction in cognitive performance.

The rationale behind the lack of changes observed during periods of reduced CBF are likely two-fold. Firstly, although indomethacin significantly reduced CBF, it is possible that the overall CD_{O_2} was not significantly reduced due to the brain's ability to increase O_2 extraction when there is a reduction in overall blood flow. As previously discussed, the brain has the ability to up-regulate O_2 extraction to match necessary demands up to a ~40-50% reduction in CBF (Bain et al., 2014). Secondly, similar to Schlader et al. (2013), who concluded that the lack of change in cognitive performance was due to the cognitive test used, the current study's results are primarily attributed to a

learning effect with the OTS task. Despite randomizing trial order, the Indo trial was conducted last for some participants. Therefore, because the OTS test was performed multiple times within each trial, it is highly likely that participants acquired a learning curve by the third experimental session.

A secondary novel finding of the current study is that $P_{ET}CO_2$ does not appear to be a contributory factor regarding any observed changes in cognitive performance during passive heat stress. Despite adequately preserving $P_{ET}CO_2$ at T-LIM in the Iso trial (42.75 ± 4.13 mmHg) vs. Poikilo trial (36.73 ± 3.59 mmHg) via end-tidal forcing, there was no significant difference in OTS accuracy or response time indices between the conditions. It is likely that despite inducing moderate hypocapnia during Poikilo, and a subsequent increase in V_e (17.59 ± 6.51 vs. 13.62 ± 3.87 $L \cdot min^{-1}$ for T-LIM and Baseline, respectively), this stressor was not enough to invoke the necessary overload demands on attentional resource recruitment.

The current findings have helped elucidate the possible effects that changes within the cerebrovasculature have on cognitive function. As with thermally-mediated effects, the proposed hypothesis was that a reduction in CBF and $P_{ET}CO_2$ may impair the ability to recruit additional neuronal resources such that a concurrent cognitive task cannot be completed as effectively. However, the results indicate that cognitive function is remarkably well preserved in spite of dynamic manipulation of cerebrovascular variables. It is likely that the manipulations of CBF and $P_{ET}CO_2$ were not the appropriate variables to induce sufficient neuronal resource demands. As previously discussed, it is probable that CD_{O_2}, the end product of CBF and Ca_{O_2}, is more likely to have a significant effect on cognitive function. To this end, it may be necessary to manipulate *both* CBF and Ca_{O_2}

concurrently (e.g. combination of indomethacin and hypoxic exposure) such that a reduction in CD_{O_2} can be ensured. Regardless, it can be concluded that CBF and $P_{ET}CO_2$ may not play an integral role in the preservation of cognitive function; however, it is more likely to be a function of CD_{O_2}. As a result of the brain's multiple protective mechanisms, the current data suggest that the brain is able to adequately sustain normal function when challenged with alterations in cerebrovascular homeostasis. To this end, it appears that the brain is much more adaptable in terms of utilizing neuronal resources during cerebrovascular changes. This is opposite to that observed during thermally-induced variations within the body, which tend to invoke a heavier demand on these neuronal resource supplies.

6.3 Technological Considerations/Limitations

The present study used TCD flowmetry to assess CBF as measured by changes in MCA_v; however, this relationship is only valid under the assumption that MCA vessel diameter remains constant. MCA vessel diameter has been shown to be unaffected by increases in ventilation (Valdueza et al., 1997) and across $P_{ET}CO_2$ ranges of ± 25mmHg from baseline (Serrador et al., 2000; Willie et al., 2012). Furthermore, TCD measurements of MCA_v have also been validated with prostaglandin inhibition during 100mg oral dose of indomethacin (Xie et al., 2006). Due to the MCA supplying ~80% of CBF to each hemisphere, it is a useful indicator of global CBF; however, due to a lack of precision regarding regional changes it is unknown whether or not there were notable increases in local CBF with subsequent cognitive activation.

The current study was also limited to measurements of $P_{ET}CO_2$ as an estimation of P_aCO_2 levels. However, previous research (Brothers et al., 2011) has demonstrated that

$P_{ET}CO_2$ accurately reflects changes in P_aCO_2. Therefore, the measured values of $P_{ET}CO_2$ in the current study accurately represent values of P_aCO_2 and observed hypocapnia accompanying prolonged heat stress.

A final consideration with regards to the current study is the repeatability of the cognitive test. The OTS test has been previously used to successfully assess executive function during passive heat stress (Gaoua et al., 2011; Gaoua et al., 2012; Schlader et al., 2015). Despite Cambridge Cognition software having multiple variations of the OTS task, in order to remain consistent within participants and between conditions, only one version was selected. Unfortunately, the OTS battery utilized does not randomize; therefore, the identical problem set is presented in the same order for every test. With subjects performing the OTS test twelve times over three experimental trials, it is very likely that they experienced a task learning effect. As such, the current results of the OTS task may not accurately represent the changes in cognitive performance that may occur during severe passive heat stress with and without concomitant changes in CBF.

6.4 Perspective and Future Directions

The current study is novel with respect to the methodological techniques used to manipulate specific variables. It is the first study to adequately separate the potential effect of CBF on executive function during passive heat stress through the use of indomethacin and end-tidal forcing. The use of indomethacin as a pharmacological intervention to selectively reduce CBF is a unique and effective method. Although severe passive heat stress has been shown to reduce CBF through hypocapnia-mediated vasoconstriction, it is likely that there are numerous confounding physiological factors that occur concurrently. Therefore, in order to specifically manipulate CBF, future

research into cognitive function should consider the use of indomethacin when attempting to examine CBF as a potential contributory mechanism.

To further current conclusions, future research should employ more in-depth physiological measurement techniques (e.g. near-infrared spectroscopy - NIRS) to achieve a better understanding of the changes occurring with similar experimental conditions. By implementing techniques such as NIRS, researchers are able to examine the actual effect on CD_{O_2}, which is likely to be a primary contributing factor. Although assessing MCA_v gives a general idea of the global CBF changes in the cerebrovasculature, we are not able to determine what, if any, fluctuations are occurring with CD_{O_2}. As previously discussed, it may be necessary for future research to include an experimental condition in which indomethacin is administered concomitantly with either hypoxia exposure or during a poikilocapnic heat stress trial in order to truly elicit a reduction in CD_{O_2}.

Future research should also ensure that the cognitive task(s) is sufficient to cause a neuronal overload in order to elicit potential performance changes. Furthermore, a varied battery of cognitive tasks should be employed in order to distinguish if any other cognitive processes are affected by changes in the cerebrovasculature during passive heat stress.

It is also important to note that the current findings of this thesis can only pertain to changes $P_{ET}CO_2$ and CBF during situations of prolonged passive heat stress. Additionally, it is unlikely, that during prolonged heat stress in typical conditions (poikilocapnia), to observe the preservation of $P_{ET}CO_2$ achieved via end-tidal forcing or the reduction in CBF achieved via indomethacin. However, it is important to note that the

current thesis was strictly looking at the potential *mechanisms* behind observed changes in cognitive performance.

6.5 Conclusions

The purpose of the present study was to examine the effect of CBF and $P_{ET}CO_2$ on cognitive function during incremental levels of passive heat stress. It was demonstrated that cognitive performance (OTS accuracy and response time) remained relatively unchanged irrespective of changes in CBF via pharmacological intervention (Indo) or preservation of $P_{ET}CO_2$ via end-tidal forcing. In contrast, improvement of OTS response time was associated with increasing intensity of passive heat stress; however, OTS accuracy indices did not significantly change as a result of increases in either $\bar{T}_{sk}$, $T_{re,}$ or both, despite inducing hyperthermia corresponding to +1.5°C above baseline T_{re}.

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Appendix A: One-Touch Stockings of Cambridge

OTS Description:

OTS is a spatial planning test variant based upon the CANTAB Stockings of Cambridge test.

This test gives a measure of frontal lobe function.

Display

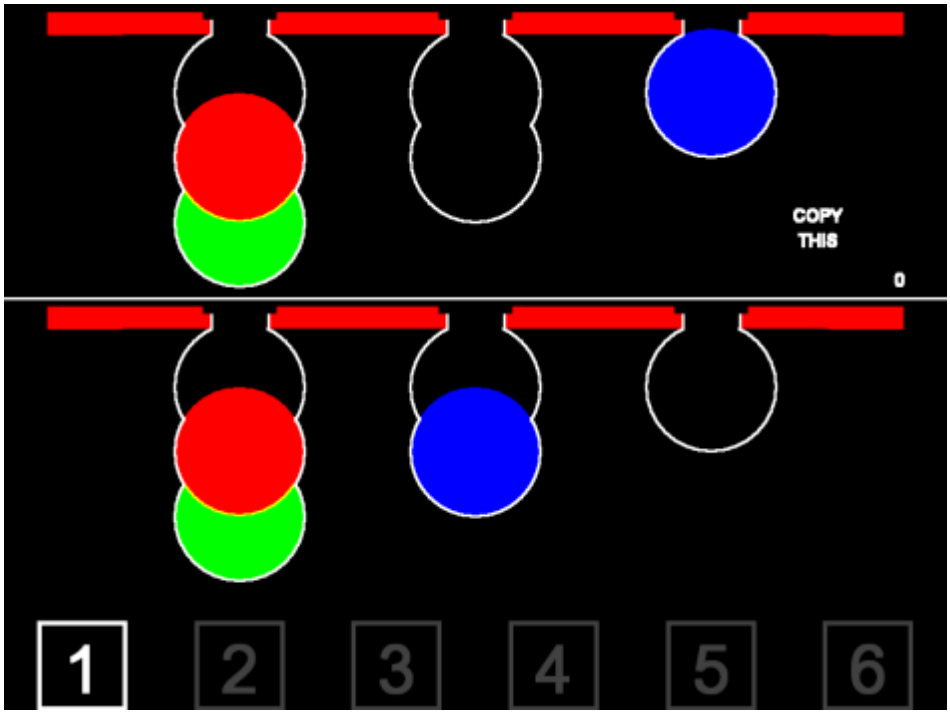

Figure. X The OTS training screen showing a 1-move problem.

The subject is shown two displays containing three coloured balls. The displays are presented in such a way that they can easily be perceived as stacks of coloured balls held in stockings or socks suspended from a beam. This arrangement makes the 3-D concepts involved apparent to the subject, and fits with the verbal instructions. There is a row of boxes containing numbers at the bottom of the screen, from one upwards.

Task

The test administrator first demonstrates to the subject how to use the balls in the lower display to copy the pattern shown in the upper display. The balls may be moved one at a time by touching the required ball, then touching the position to which it should be moved.

The subject is shown one demonstration problems, then must solve three further problems. These problems increase in complexity, from one move to four moves. If the subject makes too many moves in attempting to solve these problems, the computer presents the ideal solution to the subject (**Figure. X**).

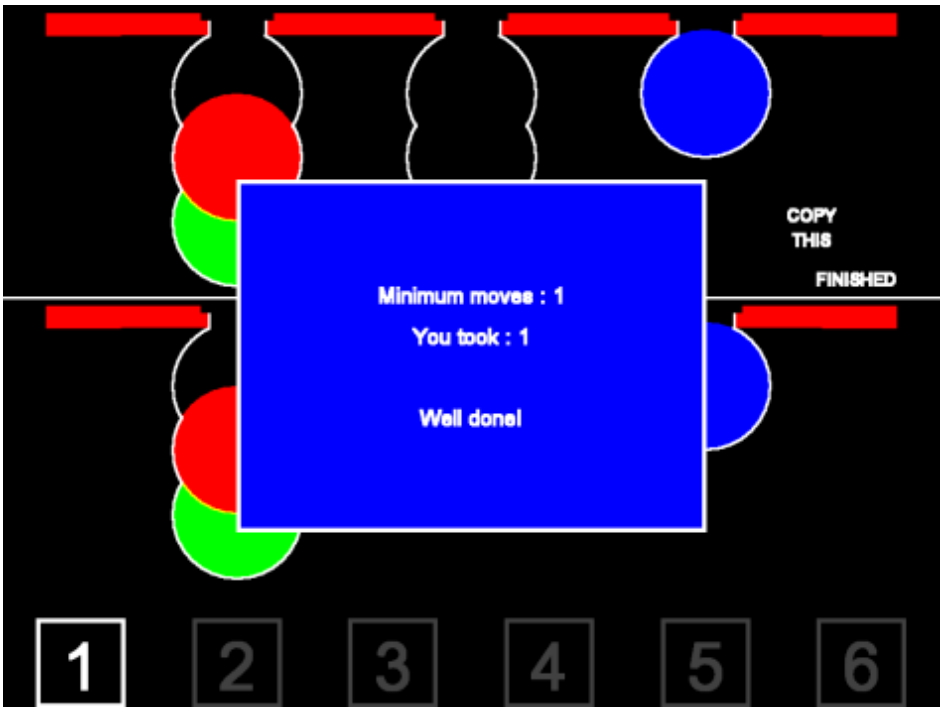

Figure. X OTS training phase after solving the first example problem

Next the subject is shown more problems, and must work out how many moves the solutions require in their head, then touch the appropriate box at the bottom of the screen to indicate the number of moves required (**Figure. X**).

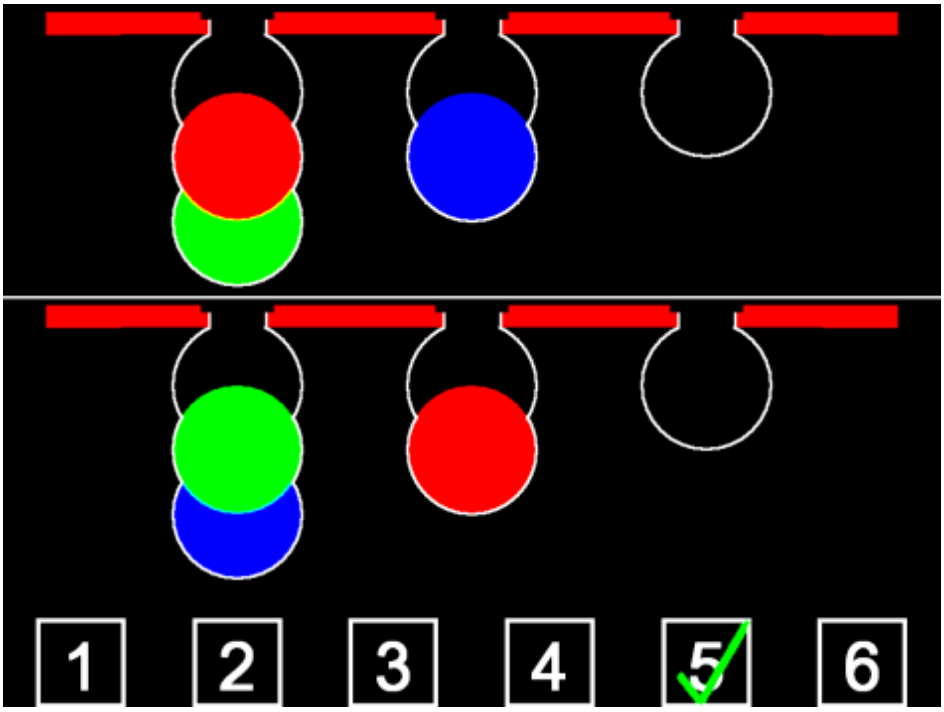

Figure. X OTS assessed phase showing a 5-move problem.

OTS test modes:

The OTS test has five modes:

- 5-choice-legacy-20
- 6-choice-20
- 6-choice-legacy-24
- 7-choice-15
- 7-choice-24

For each of these modes, the first number (5, 6 or 7) refers to the number of boxes along the bottom edge of the screen, and the second number (15, 20 or 24) refers to the number of assessed problems that the subject must solve.

For the 6-choice-20 mode, the 7-choice-15 mode and the 7-choice-24 mode, the maximum number of moves required to solve the most difficult problems in these modes is **one fewer** than the number of boxes along the bottom of the screen. Unless you have previously tested participants using these modes, we recommend that you should use the 6-choice-20, 7-choice-24 and 7-choice-15 modes only (depending on your study population).

Administration time

This test takes around eight to twelve minutes to administer.

Appendix B: Environmental Ergonomics Laboratory Screening Form

Environmental Ergonomics Laboratory Screening Form

Please read over the questions below*. They are to assist in assessing whether you are fit to participate in this study. Please ask the investigators if you have any queries before you begin filling out the form.

1.	Has your doctor ever said that you have a heart and/or cardiovascular condition (congestive heart failure, hypertension, sickle-cell anemia etc.) and that you should only do physical activity recommended by a doctor?	**YES**	**NO**
2.	Do you feel pain in your chest when you do physical activity?	**YES**	**NO**
3.	In the past month, have you had chest pain when you were not doing physical activity?	**YES**	**NO**
4.	Do you lose your balance because of dizziness or do you ever lose consciousness?	**YES**	**NO**
5.	Do you have a bone or joint problem (for example, back, knee or hip) that could be made worse by a change in your physical activity?	**YES**	**NO**
6.	Is your doctor currently prescribing drugs (for example, water pills) for your blood pressure or heart condition?	**YES**	**NO**
7.	Do you know of any other reason why you should not do physical activity?	**YES**	**NO**
8.	Do you have epilepsy or have you ever had a convulsion or a seizure?	**YES**	**NO**
9.	Have you ever had severe (i.e., followed by loss of consciousness) head trauma?	**YES**	**NO**
10.	Do you have any hearing problems or ringing in your ears?	**YES**	**NO**
11.	Are you pregnant or is there any chance that you might be?	**YES**	**NO**
12.	Do you have metal in the brain/skull (except titanium)? (e.g., splinters, fragments, clips, etc.)	**YES**	**NO**
13.	Do you have cochlear implants?	**YES**	**NO**
14.	Do you have an implanted neurostimulator? (e.g., DBS, epidural/subdural, VNS)	**YES**	**NO**
15.	Do you have a cardiac pacemaker or intracardiac lines or metal in your body?	**YES**	**NO**
16.	Do you have a medication infusion device?	**YES**	**NO**

17. Did you ever have a surgical procedure(s) to your spinal cord? **YES** **NO**
18. Do you have any spine or heart abnormalities? **YES** **NO**
19. Do you have any gastrointestinal issues (such as peptic ulcers, GI tract bleeding)? **YES** **NO**
20. Do you have any neuromuscular (e.g., epilepsy, Multiple Sclerosis, Cerebral Palsy) or skeletal (e.g., inflammatory or degenerative arthritis) disorders? **YES** **NO**
21. Do you currently have any diagnosed respiratory disease including mild asthma that may not require medication? **YES** **NO**
22. Do you have hemorrhoids? **YES** **NO**
23. Are you a smoker? **YES** **NO**
24. Do you regularly consume excessive alcohol (i.e., on average more than 3 alcoholic beverages a day)? **YES** **NO**
25. Are you a regular user of NSAIDs (such as ibuprofen, naproxen, celecoxib, etc.)? **YES** **NO**
26. Are you currently taking any medications? **YES** **NO**
    If "Yes", please list: _____
27. Do you any allergies (allergies to medications included)? **YES** **NO**
    If "Yes", please list: _____
28. Do you suffer from kidney disease? **YES** **NO**
29. Do you take Ginko herbal supplements? **YES** **NO**

Participant Name: _____

Participant Signature: _____ Date: _____

Principal Investigator Signature: _____ Date: _____

(Dr. Stephen Cheung, PhD)

Study Physician Signature: _____ Date: _____

(Dr. Matt Greenway, MD, PhD)

Appendix C: Informed Consent Form

Informed Consent

Date:

Project Title: The influence of cerebral blood flow and $P_{ET}CO_2$ on neuromuscular function during passive heat stress (EEL 073-3)

Principal Investigator: Dr. Stephen Cheung, Ph.D. (Professor)
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Co-Investigator: Dr. Matt Greenway, MD, Ph.D. (Adjunct Professor)
Department of Kinesiology, Brock University, greenwam@mcmaster.ca

INVITATION

You are invited to participate in a study that involves research. The purpose of this study is to examine the separate and combined changes in cerebral blood flow (CBF) and cerebral alkalosis (increased pH) on the ability of your muscles to produce force (neuromuscular function) with high body temperature (hyperthermia).

You may participate in this study if you are a male, 18-45 years of age, with no history of fainting, seizures or convulsions, and respiratory, cardiovascular, neuromuscular or kidney disease. You should not participate in this research if you are a smoker or have allergies to non-steroidal anti-inflammatory drugs (NSAIDS; such as advil/naproxen/celecoxib).

WHAT'S INVOLVED

There will be a total of **four** sessions. During the first session you will be screened for participation and given the opportunity to practice the experimental protocols. During the second, third and fourth sessions, blood flow to your brain will be reduced by either increasing your body temperature, your breathing rate, and/or drug manipulation. Prior to each session, you will be asked to refrain from alcohol and/or heavy exercise for 24 hours prior to the trial and caffeine on the day of the trial.

Health Screening

Before being allowed to participate, you will be asked to fill out a standard screening questionnaire detailing your current health status, use of medications and history of lung, heart, muscle and/or kidney disease. This will be done with Dr. Matthew Greenway, MD, Ph.D.

Screening Session

In the first session you will be introduced to all of the equipment being used during the experimental sessions. The protocols for each session will be explained in detail and any questions regarding the study will be answered. Subsequently, you will have your height, weight, and the amount of body fat measured. Body fat testing will be

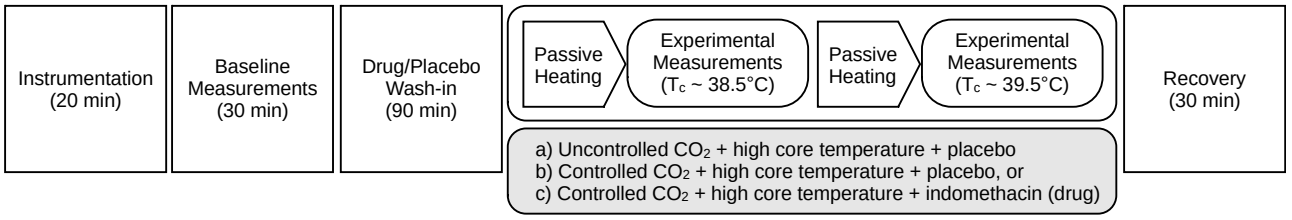
performed using skinfold calipers, which might cause a slight pinching sensation, and will be taken by someone of the same sex in a private room.

During this session you will be asked to lay down quietly while blood flow through your internal carotid artery (located in your neck) is measured using Doppler ultrasound. Similarly, blood flow velocity through your middle cerebral artery (located within your skull) will be measured. Previous research has found that only 70% of individuals have blood vessels that can be imaged using Doppler ultrasound and therefore, you may be excluded from the study if viable measurements are not obtainable.

The time commitment for the familiarization session will be approximately 90 min.

Experimental Sessions

There will be a total of **three** experimental sessions, administered in a random order, with the following protocol:



Instrumentation

During all sessions you will be required to dress only in a pair of your own shorts. You will have your internal temperature measured by wearing a rectal temperature sensor. The rectal sensor consists of a very thin and flexible plastic tube that you insert 15 cm beyond the anus. Before and after each session you will have your body weight measured and provide a small urine sample, which we will use to measure your hydration status. A euhydration threshold of ≤1.02 will be used as a cut off value. If you are above this threshold, we will ask you to consume 0.5 L of water and we will reassess your hydration status 30 min later. If you are below the defined threshold at this point, we will continue with the study. If not, we will ask you to reschedule the session for a later date to ensure your safety during the experiments.

When adequate hydration is confirmed, you will be asked to put on a liquid conditioning garment (LCG), which is similar to a diving wet suit lined with flexible PVC tubing throughout. The garment consists of a pair of pants and a jacket, leaving the head, hands, and feet uncovered. During the experiments, hot (46°C) water will be run through the tubing to increase core temperature. Skin temperature sensors will be taped onto the body surface at the following sites: forehead, abdomen, forearm, hand, quads, shin and foot, which will be used to calculate mean skin temperature.

A 3-lead electrocardiogram will monitor your heart rate. A total of three skin sites on your chest and abdomen will be shaved and swabbed with alcohol to remove any oils or dead skin cells, which may interfere with recordings. Subsequently, electrodes will be attached to these sites with adhesive disks. Your blood pressure will be measured throughout each experiment with a finger blood pressure cuff placed on your left hand. Similarly, the oxygen saturation of your blood will be measured with a pulse oximeter placed over an adjacent finger. You will wear a soft silicone facemask to collect expired gases for determining the concentration of oxygen and carbon dioxide. Every time you

exhale, the air will pass through a gas analyzer to measure the concentration of expired oxygen and carbon dioxide from your lungs. A computer controlled system will then adjust the gas levels appropriately for your next breath. This system allows the investigators to keep oxygen delivery constant under normal or hypoxic conditions while either "clamping" carbon dioxide levels at your resting values (controlled) or allowing them to fluctuate naturally (uncontrolled) throughout the experiment. You will be permitted to briefly remove the mask and drink if you require fluid during the experimental protocol. Middle cerebral artery blood flow will be measured non-invasively by a transcranial Doppler ultrasound probe placed next to your ear (temporal window) on either side of the head.

Surface electromyography (EMG) will used to measure muscle activity in the flexor carpi radialis (FCR) muscle (located in your forearm). Initially, your skin surface will be shaved, lightly abraded and cleansed with alcohol. The motor point (the most electrically sensitive region) of the FCR will be identified by placing an electrode to the backside of the forearm and using a metal probe to gently stimulate the front side of the forearm (overtop the muscle belly of the FCR) until the point at which the largest response with the least amount of voltage is identified (i.e., the motor point). Two surface EMG electrodes will be placed on the skin surface, one overtop the motor point and the other on the tendon located in the palm of the hand. A similar ground electrode will be placed on the back of the hand. This apparatus will remain connected throughout the duration of the experiment.

Baseline Measures

In addition to the above measures, your internal carotid artery and brachial artery blood flow will be measured during the baseline measurement period. Internal carotid artery blood flow will be measured non-invasively using a high-resolution ultrasound machine. You will lie on your back with a slight side tilt of the neck away from the side being scanned. Measurements will be taken on the neck below the jaw line over the duration of 10 cardiac cycles (approximately 60 seconds). Similarly, brachial artery blood flow will be measured while you lie on your back with your forearm extended in a comfortable position. Blood flow measurements will be taken in the top 1/3 of the upper arm over the duration of 10 cardiac cycles (approximately 60 seconds).

Following blood flow measures, you will perform the neuromuscular test battery. The neuromuscular test battery is comprised of the following four tests:

Motor Evoked Potential Recruitment Curve. The motor evoked potential (MEP) recruitment curve represents the ability of the brain to activate muscles at different force levels. MEPs will be evoked using a magnetic coil placed over your scalp. When activated, the magnetic coil will cause a very brief muscle twitch in your forearm. To identify the area of stimulation, a tight lycra cap will be positioned over your head. Using high stimulus intensity, the coil will be systematically moved over your scalp to determine the optimal location for eliciting a maximal amplitude MEP. Once the optimal position of the coil is established, it will be marked on the cap to ensure a constant coil placement throughout the experiment. To determine the MEP recruitment curve, stimulator intensity will be increased incrementally from the smallest observable muscle twitch by 10% increments until a maximal muscle twitch is observed.

H-Reflex. The H-Reflex is a measure of the sensitivity of your nerves that attach the spinal column to the muscle. Initially, a maximal muscle twitch will be elicited by

electrically stimulating the nerve in your forearm. Once the maximal twitch is established, the EMG activity following a 5% maximal muscle twitch will be measured.

Maximal Voluntary Contraction. A maximal voluntary contraction (MVC) represents the highest amount of force that you can produce during a muscular contraction. During MVC testing, your right arm will be secured in a custom made device used to isolate force production in the wrist. You will be asked to produce a 5-second MVC and will be verbally encouraged to maintain maximal force production throughout the duration of the contraction. EMG activity and force production will be recorded throughout the duration of your MVC. During the contraction, a maximal MEP will be elicited using identical techniques as mentioned above (see *Motor Evoked Potential Recruitment Curve*) to assess the capacity of your muscle to produce force, independent of your brain.

Sustained Maximal Voluntary Contraction: Using similar procedures as the MVC (see *Maximal Voluntary Contraction*), you will be asked to perform a sustained, 120-second MVC. You will be verbally encouraged to maintain maximal force production throughout the duration of the contraction. EMG activity and force production will be recorded throughout the duration of the sustained MVC. During the contraction, a maximal MEP will be elicited using identical techniques as mentioned above (see *Motor Evoked Potential Recruitment Curve*) to assess the capacity of your muscle to produce force, independent of your brain.

Following the neuromuscular test battery, you will then perform the One Touch Stockings of Cambridge cognitive test. During this test, you will be shown two displays each containing three coloured balls. There is a row of numbered boxes along the bottom of the screen. An investigator will demonstrate how the balls in the lower display can be moved to copy the pattern presented in the upper display. You must then complete three further problems and determine (without moving the balls) how many ball moves are required to duplicate the pattern, then touch the appropriate box at the bottom of the screen to indicate your response.

Wash-in Period

You will then perform the wash-in phase of the placebo (visits "a" and "b") or the indomethacin (visit "c"). The wash-in period will last 90 minutes allowing sufficient time for the drug concentration to peak in the blood stream. During this time, you may de-instrument and rest or work quietly in the lab.

Experimental Measures and Recovery

Following the wash-in period, you will be subjected to (a) uncontrolled CO_2 + high core temperature, (b) uncontrolled CO_2 + high core temperature or (c) uncontrolled CO_2 + high core temperature + indomethacin (drug) condition. During each condition, your core temperature will be passively increased from baseline to 39.5°C or until thermal tolerance. Experimental measures (identical to baseline measures) will be conducted when your core temperature is ~38.5°C (approximately half way through the passive heating protocol) and ~39.5°C (or whenever you feel unbearably hot). Following the attainment of each core temperature target (38.5°C or 39.5°C), the LCG will be adjusted to maintain your core temperature for the duration of the experimental measurements. Once all the experimental measures have been collected, you will de-

instrument and will be monitored for 30 minutes throughout recovery to ensure that you are symptom free from any possible side effects caused by the experimental protocol.

POTENTIAL BENEFITS AND RISKS

You will receive $100 for completion of the experiment, with payment prorated for partial completion. Your participation in this project will benefit society as you data will provide more information on the influence of changes in CBF and cerebral alkalosis on neuromuscular function that occur during environmental stress. This information is important to further our understanding of the central (relating to the central nervous system) mechanism involved in neuromuscular fatigue. Furthermore, results from this study may provide useful information for individuals who are subjected to hypoxia and hyperthermia, either in the workplace (such as military pilots and industrial workers) or because of pathology (such as chronic obstructive pulmonary disease).

There may be risks associated with participation. There will be at least two investigators trained in First Aid and CPR present for each experiment. The investigators will contact you later in the day following each session to check on your health status. Depending on your health status, you may be asked to consult with a physician. Experimental sessions will be terminated if:

1. Heart rate has risen above 95% of its maximum (220-age) for 3 min.
2. Core temperature rises above 39.5 ^{o}C.
3. Systolic blood pressure drops below 80 mmHg for more than 1 min.
4. Dizziness or nausea precludes further experimentation.
5. You decide, for any reason, to end the experiment.
6. The investigators determine that the participant is unable/unfit to continue.

Symptoms that may be experienced with hyperthermia include: discomfort, sweating, flushing and redness in the face and body, thirst, loss of fine motor coordination due to sweating, minor mental confusion, dizziness, nausea and a drop in blood pressure. Given the level of hyperthermia employed in the proposed studies ($\leq$ 39.5°C), it is unlikely that any serious symptoms would arise. In event of persistent symptoms, the heating protocol would be terminated immediately, followed by the circulation of cold water through the LCGs, allowing for the return to normothermic levels.

On rare occasion, you may unable to tolerate electrical stimulation of the nerve. Although this stimulation is not painful, the nervous system may perceive it, however brief, as harmful. As a result there is a potential for fainting. However, you will always be in a supine position during testing and therefore, the chance of injury will be remote.

Furthermore, the use of skin fold calipers may cause a slight pinching sensation. All skin fold measurements will be taken in a private room by an investigator of the same sex. Adhesive tape used to secure instrumentation may cause slight skin irritation, although this adverse response is rare. Alternative adhesive options are available if needed.

Additionally, alcohol and light abrasion used for prepping the skin for electrocardiogram and EMG recordings may leave the skin red and irritated. Moisturizer can be provided in such cases. Razors used for shaving skin area prior to

electrocardiogram and EMG electrode placement may cause minor bleeding, although in the history of EMG use in the lab this has not occurred. If bleeding does occur, appropriate first aid will be administered.

The finger cuff used for measuring blood pressure during the tests may induce some colouring at the distal end of the finger during measurements. This is not harmful to you and colouring will return within 1-2min after removing the cuff. Some people also report numbness of the finger with measurement durations exceeding 1-2hrs. Upon removal of the cuff, this feeling subsides within 1-2min.

Indomethacin

You should not ingest the indomethacin or placebo supplement if you have any dietary or religious restrictions to the consumption of animal byproducts as the capsule (for indomethacin and placebo) and contents of the placebo contain gelatin. The acute oral dose of indomethacin poses minimal risk to otherwise healthy humans. Common side effects include gastrointestinal distress, peptic ulcers, headache, dizziness and changes in kidney function; however, this is more typically associated with chronic dosage. You should not take indomethacin if you suffer from kidney disease. The incidence of other adverse reactions to indomethacin are very low (<10%) however may include myocardial infarction, stroke, high blood pressure, excessive fluid build-up in tissue, worsening of heart failure, drowsiness, tinnitus (ringing in the ears), rash, Stevens-Johnson syndrome (skin condition), nausea, shortness of breath, diarrhoea, anorexia, flatulence, bleeding in the GI tract, prolonged bleeding time, anemia (decreased red blood cells), blood dyscrasias (abnormal blood composition), elevated liver enzymes, hepatitis, anaphylactic reactions, bronchospasm (inflammation of the airway), blurred vision, decreased kidney function, kidney failure, potassium build-up, bladder inflammation and reversible female infertility. Indomethacin should not be taken if you take ACE inhibitors, angiotensin II receptor blockers, beta-blockers, cholestyramine, corticosteroids, cyclosporine, CYP2C9 Inhibitors (fluconazole, voriconazole), digoxin, diuretics, drugs that increase the risk of bleeding (anticoagulants, anti-platet drugs, heapin), lithium, methotrexate, potassium supplements, or probenecid. You should not take indomethacin if you take the herbal supplement Ginkgo.

To counteract any stomach issues (such as ulcers, acid reflux, nausea, etc.) caused by the indomethacin drug, you will be given a 150 mg antacid (such as Zantac). Although negative reactions to antacids are extremely rare, side effects include headache, general discomfort, dizziness, drowsiness, insomnia, vertigo, blurred vision, mental confusion, agitation, depression, and hallucinations, reversible involuntary movement disorders, low heart rate, high hear rate, irregular heart beats, constipation, diarrhea, nausea/vomiting, abdominal discomfort/pain, hepatitis, kidney disease, muscle and joint pain, blood count changes, rash, chest pain, bronchospasm, fever, anaphylaxis, edema, and low blood pressure. Zantac should not be taken if you take diazepam, lidocaine, phenytoin, propranolol and theophylline, triazolam, midazolam, ketoconazole, atazanavir, delaviridine, or gefitnib. Zantac may cause drowsiness therefore, you should take precaution when driving (etc.) following the trial).

Rectal Probe

When performed in a healthcare setting, insertion of the rectal probe is a controlled act as set out in the Regulated Health Professions Act. While this act does not extend to research outside of a healthcare setting, you should be aware of the following potential risks:

- Insertion of the rectal probe can stimulate the vagus nerve, which can cause slowing of the heart rate, which may lead to fainting. This is more likely to happen if you have a low resting heart rate.
- Perforation of the bowel can lead to peritonitis, a serious infection of the abdominal cavity.
- You should not participate in this research if you are pregnant, are under the influence of alcohol or other sedating substances (tranquilizers, sleeping pills, street drugs) or have any history of fainting or heart disease.

Rectal probes are classified as "single use only"; however, are commonly used multiple times by one individual without any issue. The rectal probe may become slightly discoloured during the sterilization process that occurs between lab visits. Therefore, you will be given a new rectal probe upon request or if an investigator believes that the integrity of the probe has been damaged in the sterilization process.

Transcranial Magnetic Stimulation

Although single pulse TMS is regarded as safe, the greatest acute risk is the occurrence of seizures and syncope (occurring in 1 of every 1000 studies). Other adverse effects of single pulse TMS include local discomfort at the site of stimulation, muscle soreness caused by muscle contraction, local heating and temporary hearing cause by the rapid deformation of the magnetic coils, headaches, dizziness, neck stiffness and pain. These risks are more prevalent in repetitive TMS, unlike the single pulse protocols employed in the proposed studies.

CONFIDENTIALITY

Access to this data will be restricted to Dr. Cheung and the principal student investigator, Mr. Geoff Hartley. Your participation will remain confidential. The data collected from this investigation will be kept secured on the premises of the Department of Kinesiology at Brock University in Dr. Cheung's office or laboratory, and will not be accessed by anyone other than the listed investigators.

Investigators will require disclosure of your name and contact information (phone, email), and therefore your participation is not anonymous during the conduct of the research. All participants will have their names removed from any data. The master list matching participants to data will be kept by Dr. Cheung and/or Mr. Hartley, and will be destroyed following the publication of data.

All information you provide is considered confidential; your name will not be included or, in any other way, associated with the data collected in the study. Furthermore, because our interest is in the average responses of the entire group of participants, you will not be identified individually in any way in written reports of this research.

VOLUNTARY PARTICIPATION

Participation in this study is voluntary. If you wish, you may decline to answer any questions or participate in any component of the study. Further, you may decide to withdraw from this study at any. Participation, non-participation, or withdrawal from the study will not affect your standing at Brock University.

PUBLICATION OF RESULTS

Results of this study may be published in professional journals and presented at conferences, but your personal information and participation will remain confidential. Approximately one month after we finish testing all participants, we will provide you with a summary of your own results and also the overall group results. Feedback about this study will be available from Dr. Stephen Cheung (stephen.cheung@brocku.ca, 905-688-5550x5662).

CONTACT INFORMATION AND ETHICS CLEARANCE

If you have any questions about this study or require further information, please contact the Principal Investigator or the Faculty Supervisor (where applicable) using the contact information provided above. This study has been reviewed and received ethics clearance through the Research Ethics Board at Brock University (12-271). If you have any comments or concerns about your rights as a research participant, please contact the Research Ethics Office at (905) 688-5550 Ext. 3035, reb@brocku.ca.

CONSENT FORM

I agree to participate in this study described above. I have made this decision based on the information I have read in the Information-Consent Letter. I have had the opportunity to receive any additional details I wanted about the study and understand that I may ask questions in the future. I understand that I may withdraw this consent at any time. My participation, non-participation, or withdrawal from the study will not affect my standing at Brock University.

Please note that Dr. Greenway is responsible only for your health screening and the prescription of Indomethacin (drug). All other experimental procedures are the responsibility of the Principal Investigator (Dr. Cheung).

Participant Name: _____

Participant Signature: _____ Date: _____

Principal Investigator Signature: _____ Date: _____

(Dr. Stephen Cheung, PhD)

Study Physician Signature: _____ Date: _____

(Dr. Matt Greenway, MD, PhD)

Thank you for your assistance in this project. Please keep a copy of this form for your records.